Original Article

A Histological Study of the Effect of Panax Ginseng Versus Finasteride on Induced Benign Prostatic Hyperplasia in Rats with Potentiality of Spontaneous Recovery

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ABSTRACT

Introduction: Benign prostatic hyperplasia (BPH) is a common non-malignant overgrowth of human prostate in old age that greatly affects patient's quality of life. Finasteride, one of the routinely available regimens for BPH, caused several drawbacks. Recently a natural herbal product, ginseng, had shown a promising influence on various disorders through anti-proliferative, anti-inflammatory and other beneficial effects.

Aim of the Work: To compare the effect of panax ginseng versus finasteride on BPH. Together with evaluation of the spontaneous improvement of hyperplastic features.

Materials and Methods: Fifty five adult albino rats were divided into 2 groups: control and experimental groups. BPH was induced by subcutaneous injection of testosterone (3 mg/kg/day) for 4 weeks. Then the animals were subdivided equally into 4 subgroups: BPH was sacrificed at end of 4th week, Recovery was left untreated for another 4 weeks, Finasteride & Ginseng treated subgroups received oral administration of finasteride (5 mg/kg/day) & ginseng (200 mg/kg/day) respectively for another 4 weeks. Serum DHT level and weight of prostate glands were measured. Prostatic sections were stained with toluidine blue, H&E, Masson trichrome and immunohistochemical stain for PCNA and α SMA. Additionally, the sections were subjected to morphometric and statistical analysis.

Results: BPH subgroup showed signs of hyperplasia of both epithelial and stromal cells while minimal improvement was demonstrated in the recovery subgroup. Finasteride treated subgroup showed apparent incomplete restoration of normal prostatic histological structure. While nearly normal histological architecture, biochemical & morphometric parameters were recorded in ginseng treated subgroup.

Conclusion: Ginseng proved to have a therapeutic effect superior to finasteride through its anti-mitotic, anti-inflammatory and anti-fibrotic effects. Discontinuation of testosterone administration resulted in inconsiderable regression of BPH.

Received: 23 September 2020, **Accepted:** 10 October 2020

Key Words: BPH, finasteride, ginseng, rat, testosterone.

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ISSN: 1110-0559, Vol. 44, No.3

INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common urological diseases in old men[1]. It is characterized by prostatic enlargement due to proliferation of both epithelial and stromal cells[2]. This enlargement can compress the prostatic urethra causing annoying lower urinary tract symptoms (LUTS) including intermittent urination, frequent incomplete voiding, dysuria, nocturia and urgency[3].

The definite cause of BPH remains unknown but it is obvious that androgen along with aging constitute important risk factors for cell proliferation and hyperplasia induction. Dihydrotestosterone (DHT), an androgen derived from testosterone through the action of 5α-reductase enzyme in the prostatic stromal cells, seems to be the major hormonal stimulus for cell proliferation in BPH. DHT binds to androgen receptors (AR), triggers synthesis of protein and growth of the prostatic cells[2,4]. In addition to these two factors, chronic inflammation and oxidative stress have important role in the development and pro¬gression of BPH[5].

Conventionally, finasteride a 5 α-reductase inhibitor drug is one of the main drugs used in the clinical care for BPH. However, the use of this drug has become restricted because of cost and common side effects such as dizziness, hypotension, headache, tachycardia, upper respiratory tract infection, chest pain and severe myopathy[6,7]. In addition to sexual side effects as loss of libido and impotence[8,9].

Natural herbal agents increasingly gain more importance and popularity in the treatment of BPH; because they have minimal side effects and are easy to obtain and cheap[10]. Ginseng (the dried roots of panax ginseng) is one of the most common therapeutic herbs all over the world[11]. The potential medical effects of ginseng have been related to its anti-oxidant, anti-neoplastic and anti-inflammatory activities[12].

 DOI: 10.21608/ejh.2020.43908.1360

The current work was carried out to compare the effect of panax ginseng versus finasteride on BPH induced by testosterone in adult albino rats. Besides the evaluation of spontaneous recovery of hyperplasia following termination of testosterone administration.

MATERIALS AND METHODS

I) Animals

Fifty five adult male albino rats (200 g, 12 weeks old) were housed in the Animal House of Kasr El Aini, Faculty of Medicine, Cairo University and treated in accordance with guidelines approved by the Animal Use Committee of Cairo University. They were kept in standard stainless-steel cages under standard environmental conditions (at 24 ± 1°C in normal light and dark cycle) with free access to food and water.

II-Chemicals

- Testosterone (Testolic): was purchased from T. P. DRUG LABORATORIES CO., LTD. (RAMA2 BRANCH, Thailand) in the form of testosterone propionate ampoules (100 mg/2 ml ampoule).
- Finasteride (Proscar): was purchased from MERCK SHARP & DOHME corporation company (MSD, USA) in the form of tablets (5 mg/tab).
- Panax ginseng (Ginseng): was purchased from Pharco Pharmaceuticals Company (Alex, Egypt) in the form of capsules (100 mg/cap).

III) Experimental design

Rats were randomly divided into 2 groups:

- Control group (group I): included 15 rats that were subdivided equally into 3 subgroups (Ia, Ib&Ic):
    - Subgroup Ia: rats received subcutaneous (sc) injection of 0.2 ml / day corn oil (the solvent of testosterone) for 4 weeks.
    - Subgroup Ib: rats were treated as subgroup Ia then the animals were left untreated for another 4 weeks.
    - Subgroup Ic: rats were treated as subgroup Ia then received 0.4 ml / day distilled water orally for another 4 weeks.
- Experimental group (Group II): included 40 rats. Each animal received sc injection of testosterone (3 mg/kg/day) dissolved in 0.2 ml corn oil for 4 weeks to induce BPH[13] then the animals were subdivided equally into 4 subgroups:
    - Subgroup IIa (BPH subgroup): BPH rats were sacrificed just after completion of 4 weeks testosterone treatment to confirm the hyperplasia induction.
    - Subgroup IIb (Recovery subgroup): BPH rats were left untreated for another 4 weeks.
    - -Subgroup IIc (Finasteride treated subgroup): each BPH rat received finasteride orally (5 mg/kg/day) dissolved in 0.4 ml distilled water through a gastric tube for 4 weeks[4].
    - Subgroup IId (Ginseng treated subgroup): each BPH animal was given ginseng (200 mg/kg/day) dissolved in 0.4 ml distilled water orally by gastric tube for 4 weeks[14].

IV) Experimental procedure

1-Biochemical investigation

At the end of experimental duration (4&8 weeks), blood samples were collected from the tail veins of all rats for testing the serum level of DHT. This was done at Biochemistry Department, Faculty of Medicine, Cairo University by radioimmunoassay using commercial kit from Diagnostic Products Co. (Los Angeles, CA, USA).

2- Histological studies

At Histology Department, Faculty of Medicine, Cairo University, rats from all subgroups were anesthetized by intra-peritoneal (i.p) injection of phenobarbital (60 mg/kg)[15]. The prostate glands were dissected & weighed. Specimens were obtained from the ventral lobes of prostate of all subgroups. Each specimen was divided into two parts; the first part was fixed in 10% buffered formalin solution for 24-48 hours, dehydrated in ascending grades of ethanol and embedded in paraffin. Serial sections of 6 µm thickness were cut & subjected to the following:

a. Hematoxylin & Eosin stain[16].

b. Masson trichrome stain[17].

c. Immunohistochemical staining for:

4. PCNA, a mouse monoclonal antibody (catalogue number MS-106-P, Lab Vision Corporation laboratories (Thermo scientific), Fremont, California, USA). It appears as a nuclear reaction in the proliferating cells.

5. Alpha smooth muscle actin (α SMA), a rabbit polyclonal antibody (catalogue number ABT1487, Sigma-Aldrich chemical company, Cairo, Egypt). It appears as a cytoplasmic reaction in the smooth muscle cells.

For immunostaining, sections were boiled in 10Mm citrate buffer (catalogue number AP 9003) pH 6 for 10 minutes for unmasking the antigens. Followed by cooling at room temperature for 20 minutes. Then the sections were incubated with the primary antibodies for 1 hour. Immunostaining was done using Ultravision detection system (catalogue number TP - 015- HD). Thereafter the sections were counterstained using Mayer's hematoxylin (catalogue number TA- 125-MH)[17]. Citrate buffer, Ultravision detection system & Mayer's hematoxylin were obtained from Lab Vision Thermo Scientific (Fremont, California, USA).

Small specimens from the second part were fixed in 2.5% glutaraldehyde for 2 hours. Then fixed in 1% osmium tetroxide in 0.1M phosphate buffer of PH 7.4 & 4◦C for 2 hours and embedded in epoxy resin[18]. Semithin sections were cut (1µm thickness) and stained with 1 % toluidine blue[19].

Morphometric study

The following parameters were measured:

A. Height of prostatic epithelium in H&E stained sections.

B. Area percent of collagen fibers in Masson trichrome stained sections.

C. Area percent of PCNA immunopositive cells in PCNA immunostained sections.

D. Area percent of α SMA positive immunoreactivity in α SMA immunostained sections.

All measurements were done in ten non overlapping fields (x400) from different sections of each subgroup. Image analysis was done at the Histology department, Faculty of Medicine, Cairo University using Leica Qwin 500 LTD software image analysis computer system (Cambridge, England).

Statistical analysis

The biochemical and morphometric measurements were expressed as mean ± standard deviation (SD). They were analyzed statistically using one way analysis of variance (ANOVA) followed by Tuckey post hoc test. Significant results were considered when *P value* was <0.05. Calculations were done by statistical package for social sciences (SPSS) software (version 21. IBM, Armonk. NY, USA)[20].

RESULTS

General observations

There was no mortality or morbidity in all rats throughout the experiment. Prostate glands of BPH and recovery subgroups revealed obvious enlargement by inspection.

Rats of the control subgroups (Ia, Ib&Ic) showed similar biochemical and histological results, so they were presented as control group.

Prostatic weight results (Table 1)

The mean prostatic weight recorded significant increase in all experimental subgroups except ginseng treated subgroup versus the control group. On the other hand, this value was significantly decreased in both finasteride and ginseng treated subgroups versus both BPH and recovery subgroups. In addition, finasteride treated subgroup expressed significant increase versus ginseng treated subgroup. Furthermore, non significant difference was recorded in recovery subgroup versus BPH subgroup.

Biochemical results (Table 1)

The mean value of serum DHT in BPH and recovery subgroups was significantly elevated versus the control group. After treatment with finasteride and ginseng, this value showed significant decrease versus both BPH and recovery subgroups and non significant difference versus each other and control group.

Histological results

Hematoxylin and eosin stain results

Prostatic sections of the control group showed closely packed prostatic acini of variable size and regular shape, separated by minimal fibromuscular stroma. The acini were lined by a single layer of cuboidal cells with rounded vesicular nuclei. The lumen of some acini contained an acidophilic secretion (Figures 1a,1b).

In BPH subgroup, different fields of prostatic sections illustrated widely separated acini of irregular shape, most of which were focally lined by multiple layers of disorganized cells. Papillary projections were shown protruding into the acini lumina and narrowing them. Other hyperplastic acini exhibited nearly obliterated lumina. Some epithelial cells lining the prostatic acini had pale foamy cytoplasm and pale oval nuclei, while others showed clear cytoplasm and pyknotic nuclei. The stromal spaces inbetween the prostatic acini were nearly wide, with obviously thickened fibromuscular stroma. Along with the presence of multiple congested blood vessels and intense inflammatory cellular infiltration (Figures 2a-2c).

Examination of prostatic sections of the recovery subgroup demonstrated minimal improvement of BPH histological features. In addition, congested blood vessels and intense inflammatory cellular infiltration could not be detected. However, apparently multiple cells with clear cytoplasm and shrunken darkly stained nuclei were noted lining the prostatic acini. (Figures 2d,2e).

Regarding sections of finasteride treated subgroup, some features of prostatic affection were recorded in the form of widely separated regular and irregular shaped prostatic acini with occasional thickening of fibromuscular stroma. Some acini were focally lined either by crowded cells or by multiple cellular layers forming papillary projections protruding into their lumina. While others were lined by one layer of columnar cells mostly with basal oval vesicular nuclei and others with pyknotic one (Figures 3a,3b).

Meanwhile, ginseng treated subgroup revealed nearly normal histological architecture of prostatic acini. Most of them were of regular shape and packed with apparently reduced fibromuscular stroma. The acini were lined by single layer of low columnar cells with vesicular either rounded or oval nuclei. Additionally, some epithelial cells exhibited shrunken condensed nuclei (Figures 3c,3d).

Semithin sections results

Prostatic sections of the control group revealed acini lined by one layer of cuboidal cells resting on clear intact basement membrane. The epithelial cells had rounded vesicular nuclei with prominent nucleoli and apical cytoplasmic secretory granules. Spindle shaped smooth muscle fibers were illustrated surrounding the acinar basement membranes (Figure 4).

Regarding BPH subgroup sections, most of the prostatic acini were focally lined by multiple cells resting on partially disrupted basement membranes. Acini with nearly obliterated lumina were noted. While, very few acini were lined by one layer of columnar cells. Most of the acinar cells had vesicular nuclei whereas others exhibited irregular shrunken, condensed and/or dissoluted nuclei. Along with the appearance of rarefied cytoplasm in some cells. In addition, there was detachment of epithelial cells within some lumina. Thickened connective tissue stroma and a number of mast cells with their specific metachromatically stained granules were noticed around multiple acini (Figures 5a-5c).

Recovery subgroup showed histological signs of prostatic hyperplasia similar to BPH subgroup (Figures 5d,5e).

In finasteride treated subgroup sections, prostatic acini exhibited crowded columnar cells lying on uninterrupted basement membrane surrounded by smooth muscle fibers. Additionally, some parts of acini showed focal areas of multiple cellular layers. The lining cells possessed oval vesicular nuclei with clear nucleoli and apical secretory granules (Figure 6a).

However, prostatic acini of ginseng treated subgroup demonstrated single layer of low columnar cells resting on intact basement membrane. Epithelial cells showed basal oval pale nuclei with prominent nucleoli & apical cytoplasmic secretory granules. Smooth muscle fibers were observed around the acinar basement membranes (Figure 6b).

Masson trichrome stain results

Few fine collagen fibers were noticed inbetween the prostatic acini of the control group and ginseng treated subgroup. While that of BPH and recovery subgroups were abundant thick. Regarding finasteride treated subgroup, there was moderate amount of thick collagen fibers around the acini (Figures 7a-7e).

Immunohistochemical staining results

Immunohistochemical staining for PCNA

The acinar cells showed moderate positive nuclear immunoreaction in control group and ginseng treated subgroup. While this reaction was increased in finasteride treated subgroup and became strong widely distributed in almost all cellular layers of BPH and recovery subgroups (Figures 8a-8e).

Immunohistochemical staining for α SMA

Examination of control group and ginseng treated subgroup sections exhibited a thin layer of positive cytoplasmic immunoreaction in smooth muscle cells around the prostatic acini. This positive immunoreaction appeared as thick layer in BPH and recovery subgroups. However, it was a relatively thinner in finasteride treated subgroup than BPH subgroup (Figures 9a-9e).

Morphometric results (Table 2)

The mean epithelial height, mean area percent of collagen fibers, PCNA positive cells and α SMA positive immunoreactivity recorded significant increase in all experimental subgroups except ginseng treated subgroup versus the control group. However, the mean values of the previous parameters were significantly decreased in finasteride and ginseng treated subgroups versus BPH and recovery subgroups. Moreover, finasteride treated subgroup showed significant increase in all measured parameters versus ginseng treated subgroup. In addition, there was non significant difference in all morphometric parameters in recovery subgroup versus BPH subgroup.

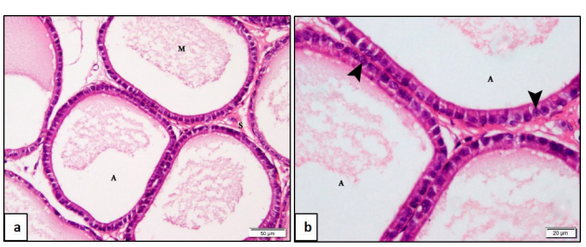

Fig. 1: Photomicrographs of H&E stained prostatic sections of control group showing: a: Closely packed regular shaped prostatic acini (A), containing an acidophilic material (M) in their lumina and separated by minimal fibromuscular stroma (S). (x 200). b: The prostatic acini (A) are lined by a single layer of cuboidal cells with rounded vesicular nuclei (arrow heads) (x 400).

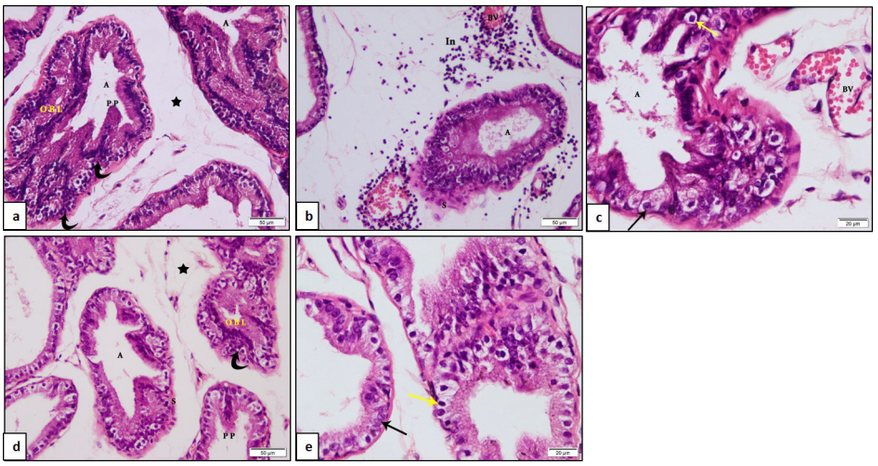

Fig. 2: Photomicrographs of H&E stained prostatic sections of BPH subgroup (a,b&c) demonstrating: a: Prostatic acini (A) of irregular shape, separated by wide stromal spaces (star). Most of the acini are focally lined by multiple disorganized cellular layers (curved arrows), some of which form papillary projections (PP) narrowing their lumina. A hyperplastic acinus with apparently obliterated lumen (OBL) can be seen (x 200). b: Intense inflammatory cellular infiltration (In) and congested blood vessels (BV) are seen surrounding prostatic acini (A) with thickened fibromuscular stroma (S) (x 200). c: An acinus (A) showed some epithelial cells with pale foamy cytoplasm and pale nuclei (black arrow) and others with clear cytoplasm and darkly stained nuclei (yellow arrow). Blood vessels (BV) can be observed (x 400). Recovery subgroup (d&e) illustrating d: widely separated prostatic acini (A) by stromal spaces (star). They are mostly of irregular shape and focally lined by multiple cellular layers (curved arrow) with papillary projections (PP) protruding into their lumina. In addition to presence of a hyperplastic acinus with nearly obliterated lumen (OBL). Areas of thickened fibromuscular stroma (S) are seen around the prostatic acini (x 200). e: Some acinar lining cells exhibit pale foamy cytoplasm and pale nuclei (black arrow) while multiple cells have clear cytoplasm and pyknotic nuclei (yellow arrow) (x 400).

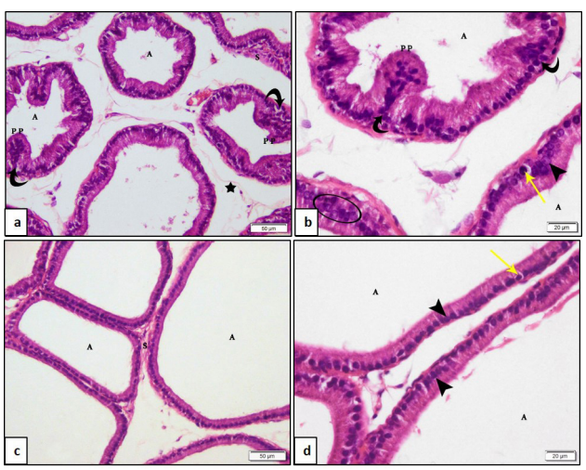

Fig. 3: Photomicrographs of H&E stained prostatic sections of finasteride treated subgroup (a&b) showing: a: Prostatic acini (A) either of regular or irregular shape widely separated by stromal spaces (star) with area of thickened fibromuscular stroma (S). Some acini are focally lined by more than one cell layer (curved arrows) forming papillary projections (PP) protruding into their lumina (x 200). b: Parts of prostatic acini (A) mostly lined by a single layer of columnar cells with basal oval pale nuclei (arrow head), however, areas of crowded cells (circle) are seen. Along with the presence of multiple cellular layers (curved arrows) forming papillary projection (PP). Some cells with densely stained nuclei (yellow arrow) are noted (x 400). Ginseng treated subgroup (c&d) illustrating c: Packed prostatic acini (A) of regular shape, separated by apparently reduced fibromuscular stroma (S) (x 200). d: Parts of prostatic acini (A) lined by one layer of low columnar cells with vesicular rounded or oval nuclei (arrow heads). Additionally, pyknotic nuclei can be noticed within some epithelial cells (yellow arrow) (x 400).

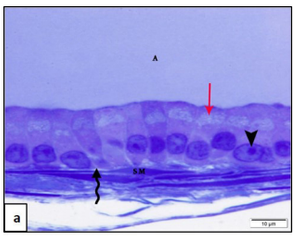

Fig. 4: Photomicrograph of control semithin section illustrating part of a prostatic acinus (A), lined by simple cuboidal epithelial cells resting on clear intact basement membrane (wavy arrow). Prostatic cells exhibit rounded vesicular nuclei with prominent nucleoli (arrow head) and apical cytoplasmic secretory granules (red arrow). Spindle shaped smooth muscle fibers (SM) are seen in close contact with the acinar basement membrane (Toluidine blue, x 1000).

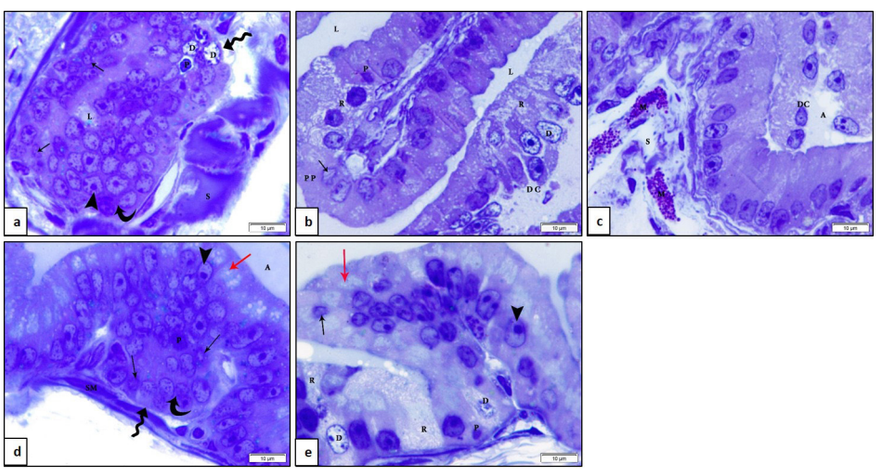

Fig. 5: Photomicrographs of prostatic semithin sections of BPH subgroup (a,b&c) illustrating: a: A prostatic acinus with nearly obliterated lumen (L) lined by multiple cellular layers (curved arrow) resting on focally disrupted area of basement membrane (wavy arrow). Most of the lining cells exhibit pale nuclei with prominent nucleoli (arrow head). While others show either irregular shrunken (thin black arrows), pyknotic (P) or dissoluted (D) nuclei. Thickened connective tissue stroma (S) surrounding the acinus is detected. b: Part of a papillary projection (PP) protruding into the lumen (L) of an acinus, exhibits some cells with rarefied cytoplasm (R). The lining cells show either pyknotic (P), irregular shrunken (thin arrow) or dissoluted (D) nuclei. Detachment of some acinar cells (DC) can be noticed. c: Multiple mast cells (M) are seen in the stroma (S) surrounding part of an acinus (A). This part is lined by single layer of columnar cells. As well as some detached cells (DC) are demonstrated within the acinar lumen. Recovery subgroup (d&e) showing d: Part of a prostatic acinus (A) lined by multiple cellular layers (curved arrow). Most of the lining cells have vesicular nuclei with clear nucleoli (arrow head) and apical secretory granules (red arrow). While other cells exhibit either irregular shrunken nuclei (thin arrows) or pyknotic one (P). Smooth muscle fibers (SM) are seen in close contact with uninterrupted acinar basement membrane (wavy arrow). e: Part of an acinus lined by cells showing vesicular nuclei (arrow head) and apical secretory granules (red arrow). While others show rarefied cytoplasm (R) and dissoluted nuclei (D). In addition, pyknotic (P) or irregular shrunken nuclei (thin arrow) can be noticed. (Toluidine blue, x 1000).

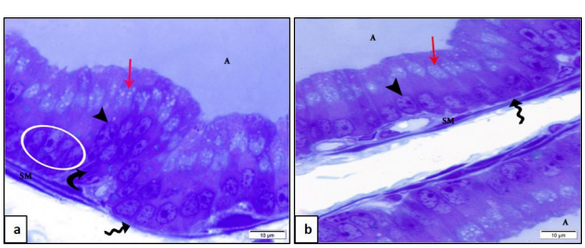

Fig. 6: Photomicrograph of prostatic semithin section of finasteride treated subgroup (a) showing part of a prostatic acinus (A) lined by focal area of multiple cellular layer (curved arrow) and areas of crowded columnar cells (circle). The lining cells exhibit oval pale nuclei with prominent nucleoli (arrow head) and apical cytoplasmic secretory granules (red arrow). Smooth muscle fibers (SM) are seen around an intact basement membrane (wavy arrow). Ginseng treated subgroup (b): illustrating parts of two prostatic acini (A) lined by a single layer of low columnar cells showing basal oval vesicular nuclei with clear nucleoli (arrow head) and apical secretory granules (red arrow). Smooth muscle fibers (SM) lie in close contact with intact acinar basement membrane (wavy arrow) (Toluidine blue, x 1000).

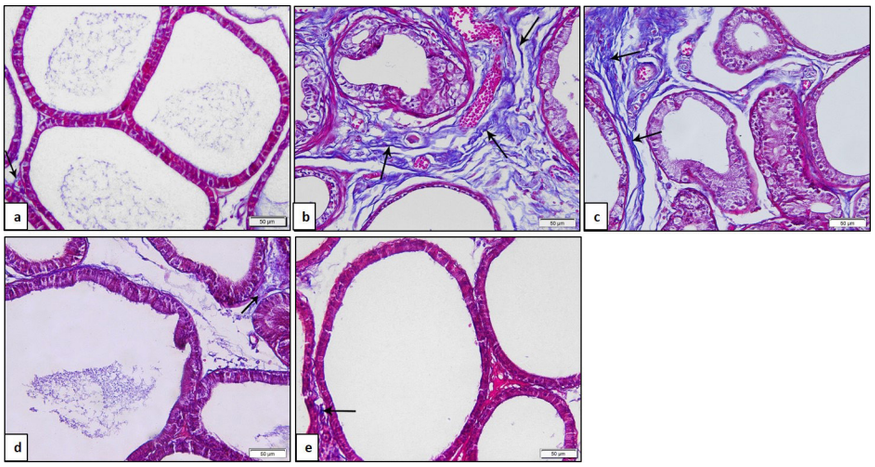

Fig. 7: Photomicrographs of Masson trichrome stained prostatic sections demonstrating: a: Control group & e: Ginseng treated subgroup illustrating few fine collagen fibers (arrow) around the prostatic acini. b: BPH & c: Recovery subgroups showing abundant thick collagen fibers (arrows). d: Finasteride treated subgroup revealing moderate amount of thickened collagen fibers (arrow) (x 200).

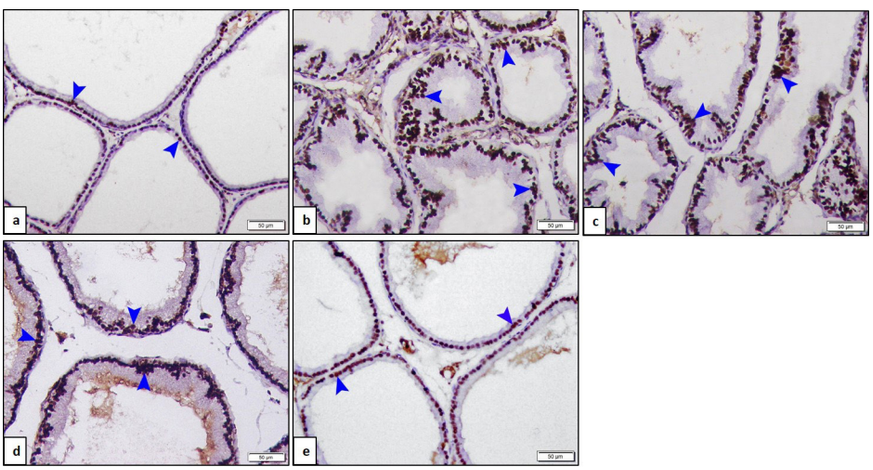

Fig. 8: Photomicrographs of PCNA immunostained prostatic sections revealing: a: Control group & e: Ginseng treated subgroup showing moderate PCNA positive nuclear immunoreaction (arrowheads) in cells lining the prostatic acini. d: finasteride treated subgroup illustrates increased positive immunoreaction. b: BPH and c: Recovery subgroups demonstrating a widely distributed strong positive nuclear immunoreaction (arrowheads) in almost all cells lining the prostatic acini (x 200).

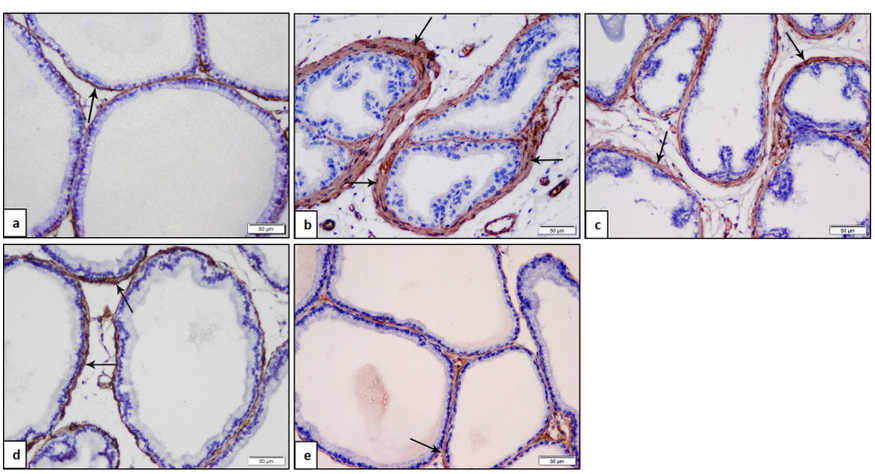

Fig. 9: Photomicrographs of SMA immunostained prostatic sections illustrating: a: Control group & e: Ginseng treated subgroup showing a thin layer of positive α SMA immunoreaction (arrow) in cytoplasm of smooth muscle fibers around the acinar basement membrane. b: BPH &c: Recovery subgroups demonstrating a thick layer of positive α SMA immunoreaction (arrows). d: Finasteride treated subgroup illustrating a relatively thin layer of positive α SMA immunoreaction (arrows) (x 200).

Table 1: Mean values ± SD of prostatic weight (g) and serum DHT level (ng/ml) of the control group and experimental subgroups.

	Control	BPH	Recovery	Finasteride	Ginseng
Prostatic weight (g)	0.8±0.07	1.82±0.01[a]	1.71±0.18[a]	1.32±0.02[abc]	0.98±0.12[b]
Mean serum DHT (ng/ml)	3.93±0.3	8.04±0.13[a]	7.5±1[a]	4.52±0.31[b]	4.3±0.21[b]

[a]significant (P<0.05) versus the control group.
[b]significant (P<0.05) versus BPH and recovery subgroups.
[c]significant (P<0.05) versus ginseng treated subgroup.

Table 2: Mean values ± SD of morphometric parameters in control group and experimental subgroups.

	Control	BPH	Recovery	Finasteride	Ginseng
Epithelial height (μm)	37.03±1.82	83.04±1.62[a]	81.78±3[a]	42.95±0.66[abc]	38.52±1.4[b]
Area % of collagen fibers	1.46±0.2	28.03±3.58[a]	25.63±2.23[a]	7.33±1.02[abc]	2.2± 0.47[b]
Area % of PCNA positive cells	3.03±0.54	18.57±3.88[a]	17.4±2.9[a]	8.47±0.23[abc]	4.74±0.43[b]
Area % of α SMA positive immunoreactivity	3.16±0.69	23.82±4.64[a]	20.9±2.54[a]	7.73±0.72[abc]	3.65±0.42[b]

[a]significant (P<0.05) versus the control group.
[b]significant (P<0.05) versus BPH and recovery subgroups.
[c]significant (P<0.05) versus ginseng treated subgroup.

DISCUSSION

Despite popularity and effectiveness of finasteride in management of BPH, various annoying side effects were reported by their use. Additionally, it needs several months of uninterrupted use to show improvement of BPH symptoms and if stopped, LUTS recur[3,21]. Thus, there was a need for other effective, natural agents achieving more compliance especially that BPH is a chronic disease. Ginseng, a phytotherapeutic agent tested in the present study was reported to be safe with no harmful adverse effects[11,22]. As well as it showed many beneficial effects such as anticancer effect[23].

Testosterone was used in the current study for experimental induction of BPH. As androgen was known as a key risk factor implicated in the pathogenesis of BPH. Added to that it was a prevalent method causing hyperplasia mainly in the ventral lobe of prostate[12,24]. The prostatic ventral lobe is the most commonly studied as it behaves like that of human prostate and it is the most androgen dependent lobe of prostate[25].

In BPH subgroup, characteristic features of hyperplasia were recorded grossly by prostatic enlargement that was confirmed by significant increase in prostatic weight compared to the control group. Histologically by widely separated hyperplastic prostatic acini with papillary projections and acini with nearly obliterated lumina. In addition, some epithelial acinar cells exhibited pale foamy cytoplasm. This might stand for the altered secretory activity of the cells. Such finding was explained previously by the consequent accumulation of hormone in the cytoplasm[4,26]. All the previous findings are in line with those of former studies which declared that epithelial stratification and increased prostatic weight are important signs of BPH development[27,28]. They attributed that to increased conversion of testosterone to DHT secondary to increased activity of 5α-reductase enzyme in BPH cells. DHT binds to nuclear AR and signals the transcription of mitogenic growth factors to both epithelial and stromal cells[7]. This was supported in the current study by significant increase in serum DHT level versus the control group. Moreover, this elevated DHT might explain the thickened fibromuscular stroma that was confirmed morphometrically by significant increase in mean area percent of collagen fibers and α SMA positive immunoreactivity versus the control group. Similar results were reported in former models[6,29]. In addition to the hyperplasia of both stromal elements (fibroblast and smooth muscles), the thickened connective tissue stroma might be attributed to the transdifferentiation of fibroblasts to myofibroblasts which synthesize the fibrillar components of stroma[12]. Meanwhile, another study found that increased stromal thickness in testosterone treated rats was mainly due to increased amount of collagen fibers more than smooth muscle[30].

The close relation and interaction between the epithelium and stroma allows the transmission of several growth factors, neuromodulators, hormones and cytokines promoting paracrine or autocrine effects and inducing a hyperplastic process[26]. Likewise it was documented that hyperplastic stroma in BPH could further trigger cellular proliferation by enhancing the expression of growth factors[12].

Additional explanation for the increased proliferation might be linked to the crucial role of stromal stem cells in the development of BPH due to imbalance between rate of proliferation and apoptosis[31]. This imbalance resulted from increased activity of telomerase enzyme in the prostatic stromal stem cells of BPH[32]. Telomerase is responsible for maintenance of telomere length through prevention of telomere shortening with each cell cycle. Under normal conditions, after each somatic cell cycle, the cell undergoes aging and apoptosis. Whereas activation of telomerase preserves genomic cell stability and promotes excessive proliferation than apoptosis[33]. This could

support the recorded significant increase in prostatic epithelial height and PCNA positive immunoreaction in BPH subgroup versus the control group.

Furthermore, other investigators associated cellular proliferation to inflammation that stimulates cell growth through oxidative stress[9,13]. Chronic prostatic inflammation with accumulation of inflammatory cells may lead to repeated tissue damage and regeneration, with increased expression of cytokines and growth factors that favors the development and progression of BPH[34]. The previous authors attributed the develop¬ment of chronic prostatic inflammation to alterations in testosterone:estrogen ratio. The aforementioned explanation could support the presence of intense inflammatory cellular infiltration, congested blood vessels and stromal edema seen around hyperplastic acini of the present study.

Such inflammation in BPH might alter the cellular junctions and result in defects of basement membrane with permeation of epithelial secretory proteins into the stroma[35]. This could explain the illustrated disrupted basement membrane and edematous widening of the stroma in the present study. Moreover, the former reporters mentioned that these secreted proteins could further stimulate a stromal reaction, causing increased cellular proliferation, inflammation and fibrosis.

The remarkable appearance of numerous mast cells in connective tissue stroma could be a part of the inflammatory response seen in BPH subgroup. The increased number of mast cells was commonly associated with areas of connective tissue remodeling occurred in different pathological abnormalities, such as inflammation and tumors[36]. Similar observation was noticed in previous BPH model[37] that considered mast cells as the main regulator of inflammatory conditions through the release of pro-inflammatory cytokines such as tumor necrosis factor alpha and angiogenic factors. In addition to expression of cycloxygenase II (COX II) that induce cell multiplication and differentiation. Reciprocally, BPH cells can affect mast cells as they allow recruitment of mast cells and stimulate their activation. This cross-link between mast cells and BPH was illustrated based on a fact that BPH stimulated the release of certain chemokine (CXCL12) from stromal and tumor cells and increased the expression of chemokine receptor (CXCR4) in mast cells[38].

As regards the acinar lining cells in BPH subgroup, most cells showed vesicular nuclei, while others exhibited either pyknotic, irregular shrunken or dissoluted nuclei with occasional rarefied cytoplasm suggesting cell apoptosis or necrosis. These two forms of cell death could be sequel of testosterone administration causing accumulation of reactive oxygen species in the prostatic tissue with subsequent oxidative stress and damaging effects on the epithelial cells. This is coincided with several studies in which elevated testosterone level in the blood caused damage in the testis, kidney and other organs[39]. Similarly other scientists recorded that apoptosis was induced during BPH development in both adult and old rats despite the growth of prostatic tissues[40]. All these assumptions supported the fact that apoptosis occurred in an attempt to cope with the uncontrolled cellular proliferation.

Moreover, the presence of epithelial cells with clear cytoplasm and pyknotic nuclei in the current model might be explained by another form of programed cell death called pyroptosis. Pyroptosis (programed necrosis) is an inflammatory host response that activates caspase 1 resulting in DNA cleavage (nuclear condensation), along with formation of pores in cell membranes, disruption of cellular ionic gradient, water influx and osmotic lysis[41]. Epithelial cells that undergoing pyroptosis will release pro-inflammatory stimuli inducing chronic inflammation with compensative growth of both epithelial cells and surrounding stromal cells, postulating another way for the pathogenesis of BPH[42].

Added to that the rarefication of cytoplasm seen in some cells could be mediated by lipid peroxidation that was closely associated with BPH[10]. Likewise, Elwan *et al*., 2018[43] illustrated a similar finding in cells of renal cortex & attributed it to lipid peroxidation. They demonstrated that lipid peroxidation caused damage of cell membrane and membranes of cell organelles resulting in an increase in their permeability and disturbance of ion concentration in cytoplasm and cell organelles. This in turn leads to dissolution of cytoplasm and swelling of these organelles with rupture of lysosomes and release of their hydrolytic enzymes in the cytoplasm causing its lysis and giving the appearance of rarefication.

Furthermore, the observed exfoliated cells in some acini of BPH subgroup was similarly demonstrated in different prostatic diseases that showed increased epithelial cells within the ejaculate[44]. This exfoliation might be linked to different stages of cell death and destruction of cell membranes by lipid peroxidation and oxidative stress. Cell membrane destruction could affect the junctions between epithelial cells causing dissociation and detachment of them into the acinar lumen[45].

Discontinuation of testosterone for four weeks in recovery subgroup showed limited improvement of histological architecture of prostatic sections. This was confirmed by the non significant difference of mean prostatic weight, epithelial height, mean area percent of collagen fibers, PCNA positive cells and α SMA positive immunoreactivity versus BPH subgroup. In the same concern, a prior model demonstrated extensive glandular hyperplasia in animals not treated for forty five days that was comparable to BPH group[10]. This might be attributed to non significant difference of serum DHT level versus BPH subgroup and could indicate that the activity of prostatic cells was maintained. Therefore, longer time might be needed to achieve lower DHT level and better recovery. Further explanation based on prostatic levels of DHT and androgen receptors remain elevated with aging condition, though the decreased peripheral levels of

testosterone therefore maintain enlarged prostate[26]. More studies demonstrated that surgical castration stimulates regression of prostate and elimination of 90% of the cells by cell death within 2 or 3 weeks[46].

Furthermore, the noticed multiple cells with clear cytoplasm and or pyknotic nuclei within the hyperplastic epithelium go in line with the minimal improvement encountered in this subgroup. This is in accordance with an early study which demonstrated that partial gland atrophy typically exhibited clear attenuated or pale cytoplasm, and nuclei that spaced apart, with few apical cytoplasm[47]. Moreover, the improvement recorded in the present work was dependent on termination of testosterone administration that caused limited decrease in DHT level than BPH subgroup giving a chance to restore normal architecture through cell death stage. Programmed cell death is a molecular mechanism driving involution of endocrine-dependent prostatic tissues in response to androgen deprivation[48]. This is in accordance with a recent study which documented that withdrawal of androgen caused partial involution of BPH[26]. This could be due to direct effects of androgen withdrawal resulting in reduction of protein synthesis, besides the activation of certain genes involved in cell death. In addition to regulation of several growth factors and their receptors[49].

In the current study, prostatic sections of finasteride treated subgroup demonstrated partial histological improvement, proved by significant decrease in prostatic weight, epithelial height, area percent of collagen fibers, PCNA positive cells and α SMA positive immunoreactivity versus BPH & recovery subgroups. On the other hand, it recorded significant increase in these parameters versus the control group and ginseng treated subgroup. The anti-proliferative effect of finasteride could be explained by inhibition of 5α- reductase enzyme that was supported by the significant decrease in DHT level versus BPH and recovery subgroups. These results are met in a previous model, which reported partial improvement of the acinar histology and reduction of the fibromuscular stroma upon finasteride treatment[4]. The former investigators also linked this amelioration to the decrease in DHT level in finasteride treated rats versus testosterone treated rats, while it did not attain the normal level of the control group. Furthermore, other studies attributed this regression to finasteride anti-inflammatory effect and anti-proliferative effect through induction of apoptosis[50,51].

Ginseng treated subgroup revealed reversed signs of hyperplasia & apparently normal histological structure of prostatic acini and fibromuscular stroma. This was enforced by the significant decrease in prostatic weight and epithelial height, area percent of collagen fibers, PCNA expression andα SMA immunoreactivity versus BPH & recovery subgroups. Along with non significant difference versus the control group. Additionally this marked improvement of prostatic epithelial & stromal hyperplasia was similarly displayed in a former study[12]. That could be explained by the ginseng anti-proliferative effect through its telomerase inhibitory activity (reducing telomere length) inducing cell death[33]. This might support the presence of some pyknotic nuclei in the lining epithelium in current work. Likewise, a previous study reported that ginseng has inhibitory activity on growth of prostate cancer cells through induction of cell death and autophagy. This is mediated via arresting of cell cycle progression by either stimulation of caspases and/or by suppression of mitogen activated protein kinase signaling pathway in cancer[52].

Another explanation for the reduced stromal elements noted in ginseng sections was assumed from a rat model of liver fibrosis induced by carbon tetrachloride which proved the anti-fibrotic effect of ginseng through down regulation of transforming growth factor beta (TGF-β) that plays a key role in synthesis of extracellular matrix proteins and fibrosis[53].

Further evidence of the resolved hyperplasia reached from the significant reduction in the level of serum DHT versus BPH & recovery subgroups. As well as the non significant difference versus the control group and finasteride treated subgroup. Similar results were reported by[12,54]. The significant reduction in DHT level could be due to decreased DHT synthesis by prostatic cells following decreased cellular proliferation. This was furtherly explained by ginseng 5α-reductase inhibitory activity in a previous study which found that red ginseng extract showed inhibitory activity against 5α-reductase[55]. The former authors tested that by topical application of red ginseng extract on shaved mice skin treated with testosterone in androgenetic alopecia model caused hair regrowth.

The determined restoration of normal histological architecture of prostatic epithelial and stromal elements was also attributed to ginseng anti-inflammatory and anti-oxidant properties. Antioxidant effect was mediated through reduction of oxygen free radicles and malondialdehyde. Added to the upregulation of the antioxidant enzymatic activity like superoxide dismutase and catalase[56]. Similarly the anti-inflammatory effect was established on cells of cancer prostate through suppression of the release of various inflammatory cytokines such as interleukin 8 (IL8), nitric oxide (NO), inducible nitric oxide synthase (iNOS) and COX II that can provoke cell proliferation and tumor development. Therefore, ginseng was supposed to be a hopeful management for different tumors[23].

CONCLUSION

Testosterone induced BPH in albino rats. Whereas limited recovery of epithelial and stromal hyperplasia was recorded upon withdrawal of testosterone administration. Ginseng proved to have a potent curative effect on BPH model compared to finasteride as it restored both the normal histological architecture and hormonal DHT level through its anti-mitotic, anti-inflammatory and anti-fibrotic effects. Proved effectiveness makes ginseng a better novel treatment for BPH.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

دراسة هستولوجية لتأثير باناكس جنسنج مقابل فيناسترايد على تضخم البروستاتا الحميد المحدث في الجرذان مع إمكانية التعافي التلقائي

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المقدمة: يعد تضخم البروستاتا الحميد ورم غير سرطاني شائع في كبار السن والذي يؤثر بشكل كبير على جودة حياة المرضى. تسبب فيناسترايد أحد الأدوية الروتينية المتاحة لعلاج تضخم البروستاتا في سلبيات عديدة. وقد اظهر جنسنج المنتج العشبي الطبيعي في الآونة الأخيرة تأثيرا واعدا على الاضطرابات المختلفة، وذلك من خلال خصائصه المضادة لتضاعف الخلايا والمضادة للالتهاب وأثاراخرى مفيده.

الهدف من البحث: مقارنة التأثير لباناكس جنسنج مقابل فيناسترايد على تضخم البروستاتا الحميد مع تقييم التحسن التلقائي لملامح التضخم.

المواد وطرق البحث: تم تقسيم خمسة وخمسين من الجرذان البيضاء البالغين الى مجموعتين: المجموعة الضابطة والمجموعة التجريبية. وقد تم احداث تضخم البروستاتا الحميد عن طريق حقن الجرذان بالتستوستيرون تحت الجلد (٣ مجم / كجم / يوم) لمدة أربعة اسابيع، ثم تم تقسيم الجرذان بالتساوي الى أربع مجموعات فرعية: تضخم البروستاتا، وتم التضحية بها في نهاية الاسبوع الرابع، التعافي، وتم تركها لمدة أربعة اسابيع اخرى دون معالجة، والمجموعتين الفرعيتين المعالجتين بفيناسترايد وجنسنج، وقد تم اعطائهما فيناسترايد (٥ مجم / كجم / يوم) وباناكس جنسنج (٢٠٠ مجم / كجم / يوم) بالترتيب عن طريق الفم لمدة اربعة اسابيع اخرى. تم قياس مستوى هرمون الدايهيدروتستوستيرون في المصل وقياس وزن البروستاتا. وقد صبغت قطاعات البروستاتا بالتلودين الازرق والهيماتوكسيلين والإيوسين وصبغة ماسون التراى كروم والصبغة الهستوكيميائية المناعية ضد α SMA، PCNAاضافة الى تعرض القطاعات للقياسات المترية الشكلية وحللت إحصائيا.

النتائج: أظهرت المجموعة الفرعية تضخم البروستاتا علامات تضخم لكلا من الخلايا الطلائية والسدوية بينما ظهر تحسن طفيف في المجموعة الفرعية التعافي. وأظهرت المجموعة الفرعية فيناسترايد حدوث استعادة جزئية ظاهرية للتركيب النسيجي الطبيعي للبروستاتا. أما المجموعة الفرعية جنسنج فقد سجلت تقريبا تركيب هستولوجى ومؤشرات بيوكيميائية وقياسات مترية شكلية طبيعية.

الاستنتاج: أثبت جنسنج ان له تأثير علاجي أفضل من فيناسترايد وذلك من خلال آثاره المضادة للانقسام، والمضادة للالتهاب والمضادة للتليف. وقد نتج عن توقف تناول التستوستيرون تراجع غير ملحوظ لتضخم البروستاتا الحميد.