Effect of Chandraprabha Vati in Experimental Prostatic Hyperplasia and Inflammation in Rats

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ABSTRACT

Chandraprabha vati, an Ayurvedic formulation, was studied for its effect in experimental prostatic hyperplasia induced by testosterone injection s.c for 21 days in rats and inflammation induced in rat hind paw by carrageenan injection s.c. The results showed that Chandraprabha vati at dosage of 100, 200 and 400 mg/kg orally for 21 days showed significant reduction of prostatic hyperplasia as indicated by decreased prostate weight and volume and histopathological observations. It also significantly inhibited carrageenan induced hind paw oedema in dose dependent manner. These results highlight the mechanism of its effect in prostate disorder like Benign Prostatic Hyperplasia (BPH) by inhibiting proliferative and inflammatory processes in prostate.

Key words: Chandraprabha vati, Ayurvedic formulation, Prostatic hyperplasia, Benign Prostatic Hyperplasia (BPH), anti-inflammatory.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is age related disorder where there is nonmalignant enlargement of the prostate due to excessive cellular growth of both the glandular and the stromal elements of the gland. BPH is usually associated with Lower Urinary Tract Symptoms (LUTS) which may present with filling symptoms (frequency, urgency, and urge incontinence) or voiding symptoms (hesitancy, poor urinary stream, straining, intermittent stream, and a feeling of incomplete bladder emptying), or both including complaints of nocturia (night-time voiding of urine). One-third of men over 50 years old reported to develop some form of LUTS with 25% of these requiring surgeries (transurethral resection) [1-8].

Prostate being an endocrinal dependent organ, hormonal imbalance; aging and androgens are main cause for the development of BPH. Hence utilization of androgen deprivation drugs affecting hypothalamic–pituitary–gonadal axis like gonadotropin-releasing hormone (GnRH) analogues, anti-androgens, and 5α-reductase inhibitors decreases the size of the prostate and the resistance to outflow through the prostatic urethra [6-8].

Prostatitis of different form is associated with BPH. It may be infectious or non infectious prostatitis. Inflammatory cells and mediators like leukotrienes, prostaglandins, and thromboxanes etc are found in prostatic secretion. Increase Urinary tract infections (UTIs) which may present with filling symptoms (frequency, urgency, and urge incontinence) or voiding symptoms (hesitancy, poor urinary stream, straining, intermittent stream, and a feeling of incomplete bladder emptying), or both including complaints of nocturia (night-time voiding of urine). One-third of men over 50 years old reported to develop some form of LUTS with 25% of these requiring surgeries (transurethral resection) [1-8].

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Some of the plants like the liposterolic extract of Saw Palmetto fruits (Serenoa repens, or Sabal serulata) [9] extracts of Stinging Nettle root (Urtica dioica L.); [10] the extract of Pygeum africanum bark; [10] have been used, singly or in combination with other botanicals for the condition of BPH. Ayurvedic formulation Chandraprabha vati is an important therapeutic medicine recommended in BPH conditions [6-8].

Chandraprabha vati formulation containing following contents was purchased from Divya Pharmacy, Haridwar, India.

Chemicals and Formulation

Chandraprabha vati formulation containing following contents was purchased from Divya Pharmacy, Haridwar, India.

Formula as per the B.R. (Bhaisajya Ratnavali)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of Ingredient</th>
<th>% content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Mustak (Curcuma longa)</td>
<td>0.92</td>
</tr>
<tr>
<td>2.</td>
<td>Devdaru (Cedrus deodara)</td>
<td>0.92</td>
</tr>
<tr>
<td>3.</td>
<td>Chitraka (Plumbago zeylanica)</td>
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</tr>
<tr>
<td>4.</td>
<td>Vidanga (Embilia ribes)</td>
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</tr>
<tr>
<td>5.</td>
<td>Marich (Piper nigrum)</td>
<td>0.92</td>
</tr>
<tr>
<td>6.</td>
<td>Pippali (Piper longum)</td>
<td>0.92</td>
</tr>
<tr>
<td>7.</td>
<td>Swarna Makshik Bhasma</td>
<td>0.92</td>
</tr>
<tr>
<td>8.</td>
<td>Daruharidra (Berberis aristata)</td>
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</tr>
<tr>
<td>9.</td>
<td>Vacha (Acorus calamus)</td>
<td>0.92</td>
</tr>
<tr>
<td>10.</td>
<td>Pimpal Mool (Piper longum)</td>
<td>0.92</td>
</tr>
<tr>
<td>11.</td>
<td>Dhanyaka (Coriandrum sativum)</td>
<td>0.92</td>
</tr>
<tr>
<td>12.</td>
<td>Gaj pippali (Piper chaba)</td>
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</tr>
<tr>
<td>13.</td>
<td>Chakav (Piper retrogastrium)</td>
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</tr>
<tr>
<td>14.</td>
<td>Sunthi (Zingiber officinale)</td>
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</tr>
<tr>
<td>15.</td>
<td>Saindhava (Rock salt)</td>
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<tr>
<td>16.</td>
<td>Ela (Elettaria cardamomum)</td>
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<td>17.</td>
<td>Chirayat (Swertia chirata)</td>
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<tr>
<td>18.</td>
<td>Haridra (Curcuma longa)</td>
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<tr>
<td>19.</td>
<td>Ativisha (Aconitum heterophyllum)</td>
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<tr>
<td>20.</td>
<td>Javakkhar (Potassium carbonate)</td>
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<tr>
<td>21.</td>
<td>Dantimool (Boliospermum montanum)</td>
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<tr>
<td>22.</td>
<td>Tejpatra (Cinnamomum tamala)</td>
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</tr>
<tr>
<td>23.</td>
<td>Twak (Cinnamomum zeylanicum)</td>
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<tr>
<td>24.</td>
<td>Vansalochan (Rambusa arundinacea)</td>
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<tr>
<td>25.</td>
<td>Lauha Bhasma</td>
<td>7.34</td>
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<tr>
<td>26.</td>
<td>Sugar</td>
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</tr>
<tr>
<td>27.</td>
<td>Purified Guggulu (Commiphora mukul)</td>
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<tr>
<td>28.</td>
<td>Purified Shilajit (Asphaltum)</td>
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<tr>
<td>29.</td>
<td>Triphala (Terminalia chebula, Emblica officinalis)</td>
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</tr>
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<td>Terminalia chebula, Emblica officinalis</td>
<td>0.92</td>
</tr>
<tr>
<td>31.</td>
<td>Kachur (Curcuma zedoaria)</td>
<td>3.66</td>
</tr>
<tr>
<td>32.</td>
<td>Kamal (Nelumbo nucifera)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

MATERIALS AND METHODS

Chandraprabha vati formulation containing following contents was purchased from Divya Pharmacy, Haridwar, India.

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All ingredients are finely powdered and mixed together and tablets are formed. Other chemicals were obtained as follows: Testosterone Propionate (German Remedies, India-Testoviron); Finasteride (Dr. Reddy, India-Finax); Carrageenan and Indomethacin from Sigma Aldrich.

**Animals**

Male rats of Sprague-Dawley strain weighing between 240-300 gm were used for the experiments. All the animals were obtained from Animal House of S.G.R.S College of Pharmacy, Saswad. The animals were fed ad libitum with standard pellet (Chakan Oil Mills, Pune, India) diet and had free access to water. All the protocols of animal experiments were approved by the Institutional Animal Ethics Committee. Animals were maintained at a temperature of 25±1°C and relative humidity of 45 to 55% under 12-h light:12-h dark cycle. They were housed individually in the polypropylene cages after surgery.

**Effect of Chandraprabha vati in experimentally induced BPH**

The rats were castrated and their testes removed. 6 days after castration animals were divided into following groups of negative control, test groups and positive control. Normal non castrated rats are taken as normal control. Negative control received testosterone propionate 0.5mg/0.1 ml by s.c route. Test groups, Chandraprabha vati, were divided in dose range of 100mg/kg, 200mg/kg and 400mg/kg and dosage was given orally. Positive control Finasteride was given at dose of 5mg/kg orally. Half hour after oral dosing the test groups and positive control group received testosterone propionate 0.5 mg/0.1 ml by s.c route. Dosing was done for 3 weeks. 24 hours after last dosing animals were sacrificed and prostate removed. Prostate weight and volume was measured. The volume was measured (by the formula: 1/2(a x b^3), where a and b refer to longer and shorter dimension, respectively) Prostate was fixed in 10% formalin. The formalin fixed tissues were embedded in paraffin and thin sections taken were stained by H & E staining process [14, 15].

**Anti-inflammatory activity of formulations**

The rats were divided into normal vehicle control, test groups, and positive control. Acute inflammation was produced by subplantar administration of 0.1 ml of 1% carrageenan in normal saline in the right paw of rats. Chandraprabha was given in dose of 100, 200 and 400 mg/kg orally. Positive control received Indomethacin 10mg/kg orally. The paw volume is measured at 0, 1, 2, 3 hours after carrageenan administration by plethysmometer (Ugo Basile). Dosing was done 1 hour before carrageenan administration. The amount of inflammation was compared with the 0 hour reading of the same rat and percentage anti-inflammatory activity calculated by comparing difference in percentage inflammation with control group [15].

**Statistical Analysis**

The data was expressed as mean ± SEM. The results were analyzed statistically using ANOVA and student’s t test. The minimum level significance was considered as P<0.05

**RESULTS**

21 days s.c injection of testosterone at dose of 0.5mg/0.1 ml significantly increased prostate weight and volume of castrated animals compared to normal animals. Chandraprabha vati, at all doses 100, 200, 400mg/kg, showed effect on volume and weight of prostate after 21 days treatment. Both Chandraprabha vati at dose of 400mg/kg and positive control Finasteride at 5mg/kg significant and comparable reduction in prostate volume and weight compared to testosterone treated (negative control) animals (Table 1).

**DISCUSSION**

Benign Prostatic Hyperplasia is a complex disease where various mechanisms are leading to enlargement of tissue and retention of urine. Age related hormonal imbalance of testosterone/estrogen and activity of testosterone and dihydrotestosterone after binding to cellular androgen receptors set complex secondary reactions that signal the cell to produce growth factors resulting in hyper plastic growth of prostate. High amounts of 5 alpha reductase enzyme activity that convert testosterone to dihydrotestosterone (active form of androgen in prostate) in prostate as well as abundance of estrogen receptor are responsible for BPH prostates [16-23].

Prostatic inflammation represents an important factor in influencing
prostatic growth and progression of symptoms. Inflammatory mediators secreted by prostatic stromal cells is mediating low level, cumulative increase in proliferation of both epithelial and stromal cells that characterizes age related development of BPH. Activation CD4+ lymphocytes, Prostate Specific Antigen (PSA) and initiation of proinflammatory processes by presence of growth factors and cytokines, autoimmune mechanisms in prostate, oxidative stress by Nitric Oxide (NO) and other oxygen species, presence of COX (Cyclooxygenase) activity leads to activation of hyperproliferative pathways in prostate. COX-2 inhibition is reported to increase apoptotic activity in prostatic cell in human BPH tissue.[42-29]

Thus, BPH may be viewed as a form of asymptomatic inflammatory prostatitis, whose pathogenesis may be triggered by a multitude of factors and pathways. Among pro-inflammatory cytokines and chemokines produced by the prostatic microenvironment, stromal-derived IL-8 may be considered a key link between chronic inflammation and stromal cell proliferation. In particular, the effect of these pathways may represent a common denominator for all 3 components of BPH: static, dynamic, and inflammatory.

Inhibition of testosterone induced proliferation in castrated rat by Ayurvedic formulation Chandraprabha vati is indicative of blockage of processes of androgen mediated growth of prostate. Secondly anti-inflammatory activity shown in carrageenan induced oedema model is indicative of inhibition of COX and prostaglandin mechanisms in prostate. This finding has initiated studies in exploration of many other Ayurvedic formulations and further mechanisms in benign prostatic hyperplasia.

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REFERENCES
23. Farnsworth WE, Roles of estrogen and SHBG in prostate physiology, Prostate, 28(1), 1996, 17-23.

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