Comparative Study of Pharmacological Activity of Afala on the Model of Hormone-Induced Prostatitis in Rats

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Afala (ultralow-dose antibodies to prostate-specific antigen) injected for 60 days to rats with hormone-induced prostatitis caused by sulpiride prevented the development of prostatic hyperplasia and reduced the severity of histological changes. The effect of Afala was superior to that of the reference drug (*Serenoa repens* extract).

Key Words: *hyperprolactinemia; benign prostatic hyperplasia; prostate-specific antigen; ultralow doses*

Benign prostatic hyperplasia (BPH) is highly prevalent in men, its incidence increasing with age. Histological signs of BPH are detected in more than 40% men over 50 years of age and in more than 90% men aged over 80. Clinical symptoms of the disease are detected in the majority of men aged over 50 [3]. Epidemiological studies carried out in Russia indicate a gradual increase in BPH incidence from 11.3% at the age of 40-49 years to 81.4% at the age of 80 [2]. The disease clinically manifests by urination disorders, significantly deteriorating the patients' quality of life [3].

Plant preparations, including those containing *Serenoa repens* extract, are widely used for the treatment of urination disorders in BPH patients [5]. Experimental studies demonstrated that *Serenoa repens* preparations prevented the development of hormone-induced hyperplasia in rats [6].

We studied pharmacological activity of afala in rats with experimental BPH.

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MATERIALS AND METHODS

Benign prostatic hyperplasia was induced by chronic injections of sulpiride (eglonil, Laboratories Synthelabo Groupe), causing hyperprolactinemia and hyperplasia of the prostatic lateral lobe [4]. Since BPH is a disease of predominantly elderly men, the study was carried out on 80 outbred male rats of the late reproductive age (8-10 months; 450-500 g).

The animals were divided into 4 groups, 20 per group. Group 1 consisted of intact animals. Animals of experimental groups received sulpiride (40 mg/kg intraperitoneally) and distilled water (5 ml/kg intragastrically, group 2); sulpiride (40 mg/kg intraperitoneally) and *Serenoa repens* (permixone, Pierre Fabre Medicament Production; 50 mg/kg intragastrically, group 3); and sulpiride (40 mg/kg intraperitoneally) and afala (5 ml/kg intragastrically, group 4) for 60 days.

After 30 and 60 days 50% animals from each group were weighed and decapitated under ether narcosis. The weights and weight coefficients of the anterior, lateral, and posterior lobes of the prostate were measured, histological study of the lateral lobe of the prostate was carried out [1] and plasma

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prolactin levels were measured by EIA using Amersham Pharmacia Biotech kits.

The data were processed using Statistica 6.0 software. The means, error of the mean, and standard deviation were calculated for each group. The means were compared using Student's *t* test for independent variables and Mann—Whitney *U* test.

RESULTS

Chronic administration of sulpiride to male rats caused hyperprolactinemia and led to prostatic hyperplasia (by day 60 of treatment) manifesting by increase in the weight coefficient of the lateral lobe of the prostate and changes in gland histology (the percent area of the glandular epithelium and the thickness of the connective tissue strata between acini increased, while acinus lumen decreased).

On day 30 of the experiment, plasma prolactin level was elevated in all animals treated with sulpiride in comparison with intact rats. On day 60 of sulpiride treatment, plasma prolactin level remained high. Afala and *Serenoa repens* treatment did not change prolactin level on days 30 or 60 of treatment (Table 1).

On day 30, the weight coefficients of the prostatic anterior, lateral, and posterior lobes of animals treated with afala and *Serenoa repens* did not differ from the corresponding weight coefficients of prostatic lobes in control and intact animals. By day 60, the weight and weight coefficients of the prostatic lateral and posterior lobes of control animals increased significantly in comparison with these parameters in intact animals. Afala, similarly as *Serenoa repens*, prevented the development of sulpiride-induced prostatic hyperplasia in rats: the weight coefficients of the prostatic anterior, lateral, and posterior lobes in the afala and *Serenoa repens* groups were significantly lower than the parameters in animals of the control group (Table 2).

Comparison of the effects of afala and *Serenoa repens* showed that afala more effectively than *Serenoa repens* prevented the increase in the weight coefficient of the prostatic lateral lobe in animals treated with sulpiride: on day 60 of the experiment, the mean weight coefficient of the prostatic lateral lobe in group

TABLE 1. Plasma Prolactin Concentration in Male Rats Treated with Sulpiride for 30 and 60 Days (*M*±*m*, pg/ml)

Duration of treatment, days	Group			
	1 (intact)	2 (control)	3	4
30	95.00±5.12	204.50±15.87*	205.60±17.53*	171.40±18.94*
60	112.60±5.03	176.20±9.09*	165.30±7.69*	182.10±8.09*

Note. *$p<0.05$ compared to intact animals.

TABLE 2. Effects of Afala and *Serenoa Repens* on Prostatic Weight and Weight Coefficients in Male Rats Treated with Sulpiride for 60 Days (*M*±*m*)

Parameter	Group			
	1 (intact)	2 (control)	3	4
Animal weight, g	532.00±8.37	514.40±8.51	509.30±16.01	501.20±18.97
Anterior lobe				
weight, mg	207.20±14.51	196.00±7.45	112.30±9.01^{+x}	75.20±5.15^{*+}
weight coefficient, mg/g	0.39±0.03	0.38±0.01	0.22±0.02^{*+x}	0.16±0.02^{*+}
Lateral lobe				
weight, mg	47.40±3.10	90.2±11.5*	38.20±5.83^{+x}	67.50±8.76^{+}
weight coefficient, mg/g	0.09±0.01	0.18±0.02*	0.07±0.01^{+x}	0.12±0.01
Posterior lobe				
weight, mg	50.40±4.46	83.40±4.90*	38.40±1.86^{+}	41.00±8.79^{+}
weight coefficient, mg/g	0.10±0.01	0.16±0.01*	0.08±0.01^{+}	0.08±0.02^{+}

Note. $p<0.05$ compared to *intact animals, $^{+}$control, ^{x}group 4.

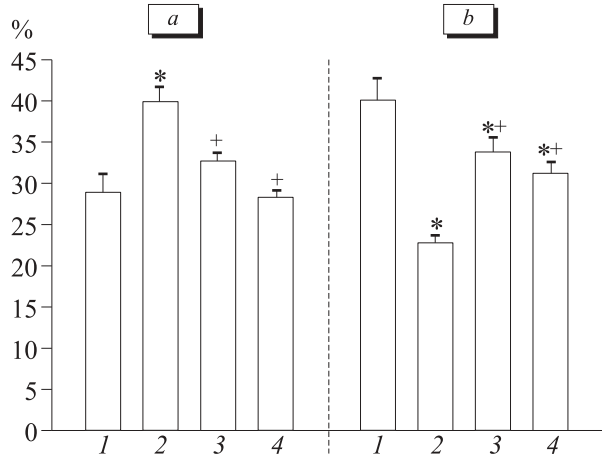

Fig. 1. Effects of afala and *Serenoa repens* on the morphology (area of structural elements) of the prostatic lateral lobe of rats treated with sulpiride for 60 days. *a*) prostatic acinus epithelium; *b*) acinus lumen. *1*) intact; *2*) distilled water+sulpiride; *3*) *Serenoa repens*+ sulpiride; *4*) afala+sulpiride. Ordinate: percent area of structural elements. $p<0.05$ compared to *intact animals, +animals treated with distilled water and sulpiride.

4 was 1.7 times lower than in group 3 (0.07±0.01 and 0.12±0.01 mg/g, respectively; $p<0.05$; Table 2).

Histological studies on days 30 and 60 showed spontaneous nodular benign hyperplasia in the prostates of 20-25% intact rats (proliferation of the acinus epithelium with the formation of papillary structures, thickening of the connective tissue between the acini), which was in line with published data and with higher incidence of BPH in elderly men. Elements of nodular BPH were detected in all rats treated with sulpiride. The number of acini with papillary epithelial growth increased. Moreover, sulpiride induced the development of focal cellular infiltration of the prostatic interstitium (with neutrophils, macrophages, lymphocytes, mast cells) and appearance of acini with dilated lumen filled with neutrophilic leukocytes. Semiquantitative histological analysis of prostatic tissues on day 60 of sulpiride treatment showed changed proportion of structural elements in the lateral lobe of the gland (Fig. 1): the percent area of glandular epithelium and interstitium increased significantly in comparison with intact animals, while the area of the acinus lumen decreased.

Both afala and *Serenoa repens* reduced the severity of sulpiride-induced changes in the prostatic structure: the area of epithelial structures decreased significantly, while the area of glandular acinus lumen increased (Fig. 1), the thickness of the connective tissue between the acini did not change, and the number of acini with leukocytes in the lumen decreased.

Hence, afala and *Serenoa repens* extract prevented the development of prostatic hyperplasia, reduced the severity of pathological changes in prostatic tissues, and did not change plasma prolactin level in male rats of late reproductive age with hormone-induced prostatitis, caused by 60-day sulpiride treatment. Afala more effectively than *Serenoa repens* prevented enlargement of the prostatic lateral lobe.

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