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# POSSIBILITIES OF PHYTOTHERAPY IN PATIENTS WITH LOWER URINARY TRACT SYMPTOMS DUE TO BENIGN PROSTATE ENLARGEMENT

© ***A.S. Al-Shukri, S.V. Kostyukov***

Academician I.P. Pavlov First St. Petersburg State Medical University of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia

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The results of the use of the phytopreparation Tadimax in the treatment of 60 men with mild and moderate lower urinary tract symptoms (LUTS) developed as a result of benign enlargement of the prostate gland are presented. The average age of the patients was 66.5 ± 3.8 years. Tadimax was prescribed 2 tablets 3 times a day, in courses of 7 days with 7 day breaks for 3 months (a total of 6 courses). The data obtained indicate high efficacy and good tolerability of treatment. A decrease in the severity of LUTS was noted in 59 (96.6%) patients, which was accompanied by significant changes in objective clinical indicators: a decrease in residual urine volume and an increase in urine flow rate. Tadimax is a combined preparation, which includes extracts of several medicinal plants, and the main component is *Crinum latifolium*. The therapeutic effect of Tadimax is based on anti-inflammatory, antiproliferative and immunotropic action.

***Keywords:*** lower urinary tract symptoms; LUTS; benign prostatic hyperplasia; BPH; benign prostate enlargement; herbal medicine; Tadimax; *Crinum latifolium*.

# ВОЗМОЖНОСТИ ФИТОТЕРАПИИ В ЛЕЧЕНИИ ПАЦИЕНТОВ С СИМПТОМАМИ НИЖНИХ МОЧЕВЫХ ПУТЕЙ ВСЛЕДСТВИЕ ДОБРОКАЧЕСТВЕННОГО УВЕЛИЧЕНИЯ ПРЕДСТАТЕЛЬНОЙ ЖЕЛЕЗЫ

© ***А.С. Аль-Шукри, С.В. Костюков***

Федеральное государственное бюджетное образовательное учреждение высшего образования «Первый Санкт-Петербургский государственный медицинский университет им. академика И.П. Павлова» Министерства здравоохранения Российской Федерации, Санкт-Петербург

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Представлены результаты применения фитопрепарата Тадимакс при лечении 60 мужчин с симптомами нижних мочевых путей (СНМП) легкой и средней степени, развившимися вследствие доброкачественного увеличения предстательной железы. Средний возраст пациентов составил 66,5 ± 3,8 года. Тадимакс назначали по 2 таблетки 3 раза в сутки, курсами по 7 дней с 7 дневными перерывами в течение 3 мес. (всего 6 курсов). Полученные данные свидетельствуют о высокой эффективности и хорошей переносимости лечения. Снижение выраженности СНМП отмечено у 59 (96,6 %) пациентов, что сопровождалось достоверными изменениями объективных клинических показателей: уменьшением объема остаточной мочи и увеличением скорости потока мочи. Тадимакс — комбинированный препарат, в состав которого входят экстракты нескольких лекарственных растений, а основной компонент представлен *Crinum latifolium*. В основе лечебного эффекта Тадимакса лежит противовоспалительное, антипролиферативное и иммунотропное действие.

***Ключевые слова:*** симптомы нижних мочевых путей; СНМП; гиперплазия предстательной железы; ДГПЖ; доброкачественное увеличение предстательной железы; фитотерапия; Тадимакс; *Crinum latifolium*.

## INTRODUCTION

Lower urinary tract symptoms (LUTS) refers to a wide range of urinary disorders, including storage, voiding, and post-micturition symptoms [1]. The incidence of LUTS in men is extremely high. Among men over 18 years of age (average age, 40.9 years) who were interviewed, 67.7% indicated the presence of urinary disorders, and the frequency

and severity of LUTS was significantly higher in the older age groups [2]. Similar data were obtained by other groups of researchers [3, 4]. The implication of LUTS is due not only to their high prevalence but also to a significant deterioration in the quality of life of patients, and a negative impact is exerted on almost all aspects of the quality of life (social, emotional, professional, sexual) [5, 6].

LUTS develop in men due to various causes and can be associated with both urinary tract and prostate diseases and with damage to the nervous system, metabolic disorders, and other factors [7, 8]. LUTS in men over 50 are most often caused by enlargement of the prostate gland due to hyperplasia [9]. Histological signs of benign prostatic hyperplasia (BPH) are relatively rarely detected in men under 45 years (up to 10%); however, by the age of 60, its detection rate reaches 60%, and by the age of 80, it is revealed in almost 80% [10]. A key pathogenetic factor in the development of LUTS in BPH is a disorder of the outflow of urine from the bladder due to infravesical obstruction [11].

It was found that BPH is due to an increase in the activity of the enzyme 5-alpha reductase, which is accompanied by an increase in dihydrotestosterone level, an active metabolite of testosterone, and an increase in the proliferation of prostate cells. The hypothesis of the hormonal nature of BPH development is recognized as valid. However, some circumstances indicate a more complex nature of BPH pathogenesis, which, in particular, is evidenced by the absence of a direct correlation between the degree of prostate enlargement and dihydrotestosterone levels [12]. In recent years, data have appeared that the second most crucial pathogenetic factor in the development of BPH is chronic inflammation of the prostate gland [13, 14]. With inflammation, infiltrates are formed in the prostate tissue, consisting mainly of T cells and macrophages. In these inflammatory infiltrates, cytokines are produced that enhance the proliferation of prostate cells. Prostate cells bordering the foci of inflammation die for unclear reasons, resulting in stromal hyperplasia in the area [15]. This outcome of inflammation on the proliferation of prostate tissue is associated with age-related weakening of the immune system, which, along with an altered hormonal status, contributes to damage to the population of suppressor cells, leading to gradual infiltration of the prostate with lymphocytes and triggering a cascade of reactions resulting in the development of BPH [16].

Both surgical and conservative methods are used to treat patients with LUTS associated with an enlarged prostate. In recent decades, a probable increase in the use of conservative therapy has been observed. Nowadays, about 85% of BPH patients are treated with drug therapy [9]. Various drugs have been proposed for the drug treatment of BPH patients. The main groups of drugs used for this purpose are represented by 5-alpha-reductase inhibitors, alpha adrenoceptor antagonists, beta 3-adrenergic agonists, muscarinic antagonists, and phosphodiesterase type 5 inhibitors; in recent years, considerable significance has been associated with the combined prescription of drugs of different groups [7, 9, 17–19]. Drug therapy for BPH is focused on the prevention of progression of the disease and the need for surgical treatment, reduction of severity of LUTS, and improvement of the quality of life of patients [7, 17]. Moreover, most authors believe that drug treatment of BPH patients can be effective only when it is pathogenetically justified [7]. Additionally, the economic aspect of treating patients with LUTS due to BPH is critical, which is associated with the high prevalence of the disease [20, 21].

Another group of drugs used to treat BPH is represented by drugs of biological (animal and plant) origin [22, 23]. Extracts of various plants for the treatment of urinary disorders associated with diseases of the prostate gland were used in the middle of the second millennium BC in ancient Egypt. The ancient Egyptian medical treatise the Ebers Papyrus, a surviving manuscript, describes the creation and use of a large number of plant-based medicines, many of which are currently still in use. The final mechanism of the therapeutic action of herbal medicinal products remains unclear; nonetheless, studies have revealed the presence of anti-inflammatory, antiandrogenic, and antiproliferative activity in plant extracts [7, 23]. However, there are no specific recommendations for the prescription of herbal remedies for the treatment of LUTS due to BPH, either alone or in combination with other drugs. This may be due to the difficulties in assessing the pharmacokinetics and pharmacodynamics of herbal medicines, as well as a wide variety of both the initial substrates and their production technology. However, despite this, phytopreparations for the treatment of BPH are widely used in Russia and in other countries, and their efficiency and good tolerance in this category of patients has been confirmed by clinical studies [7, 23, 24].

One of the herbal remedies used to treat patients with LUTS due to BPH is Tadimax. The drug Tadimax was produced based on the medicinal plant *Crinum latifolium*, a perennial herb of the Amaryllis family. The genus *Crinum* (lat. *Crinum*) includes about 130 species of plants, several of which have long been widely used in folk medicine in various regions worldwide, mainly in China, Korea, and Vietnam, for the prevention and treatment of prostate gland diseases [25]. Extracts from plants of the genus *Crinum* have a unique range of biological activity manifested by antitumor, immunostimulating, analgesic, antiviral, antibacterial, and antifungal effects, which are mainly attributed to alkaloids of the *Amaryllidaceae* family, several of which are found only in plants of the genus *Crinum* [26–28]. Lycorin, the most famous of these alkaloids, has a pronounced antiproliferative activity, manifested in the enhancement of apoptosis of tumor cells and inhibition of RNA replication in them [29]. Studies performed in the last decade have revealed that *Crinum latifolium* induces a dose-dependent anti-inflammatory, antiproliferative, and immunotropic effect, which can be considered as the pathogenetic basis of its antitumor effect [30].

Additionally, *Crinum latifolium*, which is the main plant substrate of the herbal preparation Tadimax, contains a number of other components with high biological activity, including rhizomes of anemarrhena (*Rhizomata Anemarrhenae*), bark of Amur cork tree (*Cortex Phellodendri*), herb of Japanese motherwort (*Herba Leonuri japonici*), rhizome of alismatis (water plantain, *Rhizomata Alismatis*), roots of peony (*Radicis Paeoniae*), bark of cinnamon (*Cortex Cinnamomi*), and peach seeds (*Semen Persicae*).

Clinical cases have shown the feasibility of Tadimax in patients with LUTS due to BPH. In a study by Nusratulloeva et al. [31], Tadimax was prescribed in 30 patients with BPH (2 tablets, 3 times a day after meals for 7 days, followed by a 7-day break). The course of treatment, lasting 6 weeks, consisted of three similar cycles. A positive clinical effect from the therapy was noted in all 18 BPH patients in the compensated stage and in 9 out of 12 patients in the subcompensated stage.

In another study by Chaika et al. [32], 95 men aged 47–72 years were under follow-up: 33 BPH patients constituted the main group, 32 patients the comparison group, and 30 healthy men the control group [32]. The study included patients with BPH who had no indications for surgical treatment. The patients in the main group received herbal drug Tadimax according to the standard regimen (2 tablets, 3 times a day for 7 days with 7-day intervals for 3 months), and those in the comparison group received traditional therapy. During treatment, the severity of dysuric disorders in men of the main group significantly decreased by 2.8 times according to the IPSS questionnaire, the quality of life increased, the volume of the prostate decreased by 1.2 times according to the data of transrectal ultrasound (TRUS), and the volume of residual urine decreased by 2.1 times. The dynamics of clinical indicators was comparable with the results obtained in the comparison group. Moreover, better tolerability of Tadimax treatment compared to traditional therapy was noted. Due to revealed therapeutic efficacy and good tolerability of the drug, the authors recommended Tadimax for widespread use in men with LUTS that develop with the presence of BPH [32].

Despite the wide range of biological activity of the plant components that make up Tadimax and the pathogenetic justification of its use in BPH patients, there are relatively few publications on its use in this category of patients. This determined the relevance of this study.

*The present study aimed* to assess the efficacy and tolerability of the phytopreparation Tadimax in the treatment of patients with BPH manifested clinically by LUTS of mild to moderate severity.

## MATERIALS AND METHODS

Furthermore, 60 men with BPH, clinically manifested by mild to moderate LUTS, were under supervision in the clinic of urology of the First Pavlov Saint Petersburg State Medical University. The average age of the patients was 66.5 ± 3.8 years. The criteria for inclusion in the study were age ≥50 years, the presence of complaints of urinary disorders, the maximum volumetric urinary flow rate of >5 and <12 ml/s with a volume of urination of at least 125 ml, the volume of residual urine according to ultrasound (US) of not more than 150 ml, IPSS more than 12 points, and the prostate volume according to TRUS data more than 30 $cm^3$. The study did not include patients with indications for surgical treatment of BPH, the presence of causes other than BPH for the occurrence of infravesical obstruction and LUTS, neurogenic dysfunctions of the lower urinary

tract, acute or exacerbated infectious and inflammatory diseases of the urinary tract and prostate gland, the presence of cystic calculi, and malignant tumors of the urinary and male genital organs. Moreover, the exclusion criteria were a history of pelvic surgery, radiation therapy, and intake of drugs that affect the function of the lower urinary tract for 2 weeks before the start of the study. All the patients examined received Tadimax per os after meals, two coated tablets, 3 times a day for 7 days with 7-day intervals for 3 months (a total of six courses). The examination of patients conducted before the start of treatment and at weeks 4, 8, and 12 following treatment included an assessment of the severity of LUTS on the IPSS scale, assessment of the quality of life on the QoL scale, blood test for prostate specific antigen (PSA), uroflowmetry with the determination of the maximum urine flow rate ($Q_{max}$), transrectal ultrasound of the prostate, and the bladder US with the determination of the volume of residual urine. In sexually active 36 (60%) patients, erectile function was assessed using the IIEF-5 (International Index of Erectile Function) questionnaire. Tolerance was assessed by the frequency and severity of adverse events. All the data obtained were entered into a special research record. The calculation and statistical analysis of the research results were performed using the Statistica 10.0 software. Differences were considered significant at a significance level of $p \leq 0.05$. The mean values of the indicators in the text were indicated with the mean-square deviation ($M \pm \sigma$).

## RESULTS AND DISCUSSION

The data obtained indicate that the use of Tadimax resulted in a decrease in the severity of LUTS and an improvement in objective parameters. It was noted that statistically significant positive dynamics of clinical indicators was determined by week 8 of treatment (Table 1). By this time, in 58 (96.6%) of 60 patients monitored, a decrease in the intensity of urination disorders was observed, which was manifested by a decrease in the number of daytime and nighttime urination, an increase in the interval between urinations, and an increase in the urine stream. After another 4 weeks, that is, by week 12 from the start of treatment, an even greater decrease in the severity of symptoms was seen. By the end of therapy, the sum of points on the IPSS questionnaire decreased in comparison with the initial value by 45% (from 20.0 ± 1.2 to 11.0 ± 1.5, $p < 0.05$) and the quality of life on the QoL scale improved on average by 45.2% (from 3.8 ± 0.4 to 2.2 ± 0.1, $p < 0.05$). Subjective improvement was confirmed by positive dynamics of objective indices. The residual urine volume decreased by 43.5%, that is, from the initial 63.4 ± 11.3 to 35.8 ± 9.7 ml ($p < 0.05$). The maximum urine flow rate according to uroflowmetry data increased by 51.6%, from 9.3 ± 1.3 to 14.1 ± 0.5 ml/s ($p < 0.01$). In addition, 14 (38.9%) out of the 36 sexually active patients who filled out the IIEF-5 questionnaire noted an improvement in erectile function. The sum of points on the IIEF-5 scale was 17 ± 4.1 before the start of treatment and increased

*Table 1 / Таблица 1*

**Results of treatment for patients with lower urinary tract symptoms due to benign prostatic enlargement with herbal drug Tadimax, $M \pm \sigma$ ($n = 60$)**

**Результаты лечения фитопрепаратом Тадимакс пациентов с симптомами нижних мочевых путей, вызванных доброкачественным увеличением простаты, $M \pm \sigma$ ($n = 60$)**

| Criteria for evaluating treatment outcomes | Baseline indicators | 4 weeks | 8 weeks | 12 weeks |
|---|---|---|---|---|
| I-PSS questionnaire, points | 20.0 ± 1.2 | 18.0 ± 1.5 | 15.0 ± 2.5 ** | 11.0 ± 1.5 ** |
| QoL scale, points | 3.8 ± 0.4 | 3.5 ± 0.4 | 2.8 ± 0.2 ** | 2.2 ± 0.1 ** |
| IIEF 5 scale, points | 17.0 ± 4.1 | 16.2 ± 3.3 | 18.0 ± 3.6 * | 19.4 ± 1.5* |
| Maximum urine flow rate ($Q_{max}$), ml/s | 9.3 ± 1.3 | 9.2 ± 1.2 | 11.1 ± 0.3 * | 14.1 ± 0.5 * |
| Residual urine volume, ml | 63.4 ± 11.3 | 62.1 ± 12.4 | 45.3 ± 10.1 ** | 35.8 ± 9.7 ** |

* The difference in indicators before and after treatment is significant ($p < 0.0.05$); ** the difference in indicators before and after treatment is significant ($p < 0.01$).

to 19.4 ± 1.5 ($p < 0.05$) after. The absence of positive changes in the severity of clinical manifestations of LUTS was indicated by only one (1.7%) patient. The treatment was tolerated well, and none of the patients monitored interrupted the course of treatment. An adverse event (diarrhea) associated with the intake of the drug was noted in only one (1.7%) patient. After a thorough survey, 3 (5%) patients indicated an improvement in the act of defecation, a decrease in the severity of constipation. When questioning with the Bristol scale of feces, the numerical value on this scale in these patients increased on average from 1.7 to 3.5. Four (6.7%) patients indicated a decrease in discomfort, burning during and after intercourse. The mechanism of action of the therapy on these conditions is unclear and requires additional research. When analyzing the TRUS data, we did not notice any change in the volume of the prostate gland before and after treatment with the herbal drug Tadimax.

Thus, our data indicate the efficiency and safety of the use of Tadimax in the treatment of patients with LUTS due to BPH. Nevertheless, positive dynamics was noted only by the end of month 2 of treatment. The absence of such in the earlier periods of therapy indicates the delayed nature of the action of Tadimax. The efficiency of treatment was 96.6%, which was confirmed not only by changes in the patients' complaints in time but also by significant positive changes in objective clinical indices such as a decrease in residual urine volume and an increase in urine flow rate. We believe that the therapeutic effect of Tadimax is based on the previously identified anti-inflammatory, antiproliferative, and immunotropic action of the drug [30].

## CONCLUSION

The results of the study confirm the high efficiency and significant tolerability of the use of Tadimax in patients with LUTS associated with benign prostatic enlargement of mild to moderate severity.

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*Information about the authors:*

**Adel S. Al-Shukri** — Dr. Sci. (Med.), Professor, Head of the Urological Division No. 1 (General and Urgent Urology) of the Research Center of Urology, Research Institute of Surgery and Emergency Medicine. Academician I.P. Pavlov First St. Petersburg State Medical University of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia. E-mail: ad330@mail.ru.

**Stanislav V. Kostyukov** — Clinical Resident of Department of Urology. Academician I.P. Pavlov First St. Petersburg State Medical University of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia. E-mail: stanislav.kostyukov57@mail.ru.

*Сведения об авторах:*

**Адель Сальманович Аль-Шукри** — д-р мед. наук, профессор, руководитель урологического отделения № 1 (общей и неотложной урологии) Научно-исследовательского центра урологии НИИ хирургии и неотложной медицины. ФГБОУ ВО ПСПбГМУ им. акад. И.П. Павлова Минздрава России, Санкт-Петербург. E-mail: ad330@mail.ru.

**Станислав Вадимович Костюков** — клинический ординатор кафедры урологии. ФГБОУ ВО ПСПбГМУ им. акад. И.П. Павлова Минздрава России, Санкт-Петербург. E-mail: stanislav.kostyukov57@mail.ru.