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PROSTATIC BIOREGULATORY POLYPEPTIDE PROSTATILEN: PHARMACOLOGICAL PROPERTIES AND 30-YEAR EXPERIENCE OF CLINICAL APPLICATION IN UROLOGY

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The review summarizes the results of 30-year clinical application of the prostatic bioregulatory peptide Prostatilen. The data from experimental studies, testifying for the high biological activity of the drug is shown, the mechanisms of its therapeutic action are described. The review presents the results of clinical studies demonstrating the effectiveness and pathogenetic justification of the prescription of Prostatilen in the treatment of chronic prostatitis, benign prostatic hyperplasia, infectious and inflammatory diseases of kidneys and urinary bladder, as well as of several other diseases. The experience of Prostatilen application in the urological clinic of First Pavlov Saint Petersburg State Medical University is shown.

Keywords: chronic prostatitis; benign prostatic hyperplasia; pyelonephritis; cystitis; male fertility; prostate peptides; Prostatilen.

ПРОСТАТИЧЕСКИЙ БИОРЕГУЛЯТОРНЫЙ ПОЛИПЕПТИД ПРОСТАТИЛЕН: ФАРМАКОЛОГИЧЕСКИЕ СВОЙСТВА И ОПЫТ 30-ЛЕТНЕГО КЛИНИЧЕСКОГО ПРИМЕНЕНИЯ В УРОЛОГИИ

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В статье подведены итоги 30-летнего клинического применения биорегуляторного пептида предстательной железы Простатилена. Приведены данные экспериментальных исследований, свидетельствующие о высокой биологической активности препарата, описаны механизмы его лечебного действия. Представлены результаты клинических исследований, демонстрирующие эффективность и патогенетическую обоснованность назначения Простатилена при лечении хронического простатита, доброкачественной гиперплазии предстательной железы, инфекционно-воспалительных заболеваний почек и мочевого пузыря и ряда других болезней. Показан опыт применения Простатилена в клинике урологии ПСПбГМУ им. акад. И.П. Павлова.

Ключевые слова: хронический простатит; доброкачественная гиперплазия предстательной железы; пиелонефрит; цистит; мужская фертильность; пептиды предстательной железы; Простатилен.

INTRODUCTION

The use of extracts obtained from animal tissues for therapeutic purposes originates deep in the past. For many centuries and millennia, representatives of all known civilizations have used them as medicines. In traditional Chinese medicine, more than 1,500 of the medicines used are of animal origin, and many of them are described in ancient

Indian treatises on Ayurvedic medicine. Various extracts and humors of biological origin were used by the healers in Ancient Egypt and pre-Columbian America. Among the early Slavs, medicines based on animal tissues also had an important role among healers. In 1778, the first Russian pharmaceutical register, Pharmacopoea Rossica, was created, and a significant part of the register described medicines of animal origin. This can be considered as their recognition by the official national medicine [1]. The first scientific studies of the effectiveness of animal tissue extracts were conducted in the XIX century and were related to the French physiologist Ch. Brown-Sequard, and the famous Russian scientist I.I. Mechnikov, who studied the biological properties of spermine. This term denoted substrates obtained from the tissues of the testes, ovaries, spleen, and other organs.

GENERAL PRINCIPLES OF PEPTIDE REGULATION OF BIOLOGICAL PROCESSES AND MECHANISMS OF BIOLOGICAL ACTIVITY OF REGULATORY PEPTIDES

Hundreds of medicinal preparations of animal origin are currently used for therapeutic purposes, and bioregulatory peptides hold an important place among them [2]. They were first studied in 1970s, when Russian researchers V.Kh. Khavinson and V.G. Morozov developed a method to obtain special biologically active substances of peptide nature, cytomedins, from animal tissues [3]. Subsequently, it was revealed that such substances are present in almost all organs and tissues, that they belong functionally to the mediator link of the bioregulation system, and that their biological activity is determined by specific oligomeric molecules consisting of amino acids, namely low molecular weight peptides [4]. Further studies demonstrated the regulatory effect of cytomedines on various physiological functions; therefore, they were attributed to the class of regulatory peptides.

The theory of regulatory peptides is based on the concept of peptide regulation of physiological processes proposed by the outstanding Russian physiologist and biochemist I.P. Ashmarin. According to this concept, peptide regulation is considered the most important and ancient mechanism for coordinating vital activity, and is part of the process of evolution of multicellular organisms, where the peptides themselves are carriers and transmitters of intercellular information [5]. Regulatory peptides are polyfunctional, while each type of molecule has its own special unique program that determines both their direct action as activators or inhibitors of physiological processes, and the ability to induce the release of other substances with similar properties. After the synthesis of endogenous regulatory peptides or the administration of exogenous regulatory peptides, new portions of biologically active substances are released, which in turn initiate the release of the next group of peptide regulators. Thus, a process is formed, designated as "peptide cascade." As a result, peptide bioregulation has exceptional flexibility and enables the formation of the required amount of the necessary regulatory substances in a short time in the proper place [6].

The use of bioregulatory peptides in clinical practice has an essential scientific substantiation. The most important aim of the therapeutic effect is correction of the functional activity of cells in the desired direction. The function of intercellular mediators is performed by both secretory proteins, cytokines, and peptide bioregulators that maintain the structural and functional homeostasis of cell populations [7]. The mechanism of biological activity of bioregulatory peptides at the molecular level can be represented as follows: Oligomeric peptides enter the cell nucleus through the cytoplasm and the nuclear membrane. The complementary interaction of these peptides with the promoter zones of genes signals for transcription, translation, and synthesis of proteins on ribosomes. These processes contribute to a change in the function of various organs and tissues, thereby providing the necessary therapeutic effect [8].

The use of exogenous peptide bioregulators for therapeutic purposes has a number of unique aspects. On the one hand, their therapeutic effect is

not limited by the time of the drug intake. Due to the peptide cascade, the therapeutic effect persists for a long time after the drug is administered. A relatively short 5–10-day course of treatment can trigger a cascade reaction lasting 2 months, 4 months, or even up to 6 months, according to some reports. Another characteristic of the clinical use of peptide bioregulators is that their final effect does not increase with an increase in the amount of peptide preparation administered, since for each peptide, there is a certain limit after which an increase in the dose does not increase the clinical effect [9]. This effect is due to the cascade principle of bioregulation, in which a certain, usually insignificant, amount of substrate is sufficient to trigger a chain reaction. The presence of a peptide regulatory cascade is also associated with the absence of dose-dependence of the effects of regulatory peptides, when a drug prescribed in a minimum dose can contribute to the achievement of significant clinical results.

Initially, peptide preparations of animal origin were supposed to be used only to restore and normalize the function of the organs and tissues from which they were obtained. Subsequently, it was revealed that these peptides also have a significant systemic effect on the most important physiological processes, at the cellular and molecular levels [3]. For this reason, tissue peptide extracts subsequently became known as bioregulatory peptides. This emphasized the possibility of their participation in the regulation of the basic physiological processes of the human body, namely differentiation and proliferation of cells, development and aging of the body, and the exchange and reproduction of genetic information.

PHARMACOLOGICAL PROPERTIES OF PROSTATIC PEPTIDE DRUG PROSTATILEN

Nowadays, in clinical practice, peptide preparations from the thymus gland, cerebral cortex, and a number of other organs and tissues are used; however, drugs based on the prostate gland are the most widespread. Prostatic peptides were first obtained in the mid-1980s from the bovine prostate gland [10]. Like other bioregulatory peptides, they lacked species-specificity; however, pronounced tissue specificity was revealed; in this case, tropism for prostate tissue. Therefore, having a significant systemic effect, prostatic peptides have the ability to influence to the greatest extent on their target organ, the prostate gland. Subsequently, the pharmaceutical form of the drug, Prostatilen, was created by ultrafiltration of the prostatic peptide complex.

The results of the first experimental studies revealed a variety of biological properties in Prostatilen, which were later clinically confirmed. Anti-inflammatory and immunotropic effects were found, as well as the ability to improve hemodynamics and rheological properties of blood, and a direct myotropic effect [11–16].

The effect of the prostate preparation on the state of microcirculation is due to several factors. Prostatilen has a hypocoagulatory effect and reduces the extent of platelet aggregation [10, 11]. In the experiment, the administration of Prostatilen for 1 week resulted in a significant increase of the blood coagulation time, and an increase in antiaggregatory activity of the vascular wall [11]. Prostatilen interferes with platelet adhesion in case of endothelial damage, and leads to a decrease in platelet aggregation. Prostatic peptides also directly influence thrombogenesis. The incidence of venule thrombosis in experimental animals and the cross-sectional area of thrombi were found to be significantly lower under the influence of Prostatilen than in the control group [11, 12, 17]. An increase in thromboresistance of venules is possibly associated with the effect of regulatory peptides on prostacyclin biosynthesis in the vascular wall [18]. In addition, the prostatic peptides have the ability to enhance the blood fibrinolytic activity [19]. Thus, the effect of prostatic peptides on the hemostatic system is due to the effect both on the processes of blood coagulation and fibrinolysis, and on the platelet-vascular mechanism. These effects determine the ability of Prostatilen to restore the rheological properties of blood and improve microcirculation in the affected organs. The normalization of hemodynamics is the most important

factor in successful treatment of inflammatory diseases.

Prostatilen also has a direct anti-inflammatory effect. On the one hand, it is because of Prostatilen's ability to enhance the synthesis of antihistamine and antiserotonin antibodies [13]. Another possible reason for the anti-inflammatory effect of prostate extracts is the supposed presence of agents that inhibit MCP-1-stimulated cell migration. MCP-1 (monocyte chemotactic protein-1) is one of the main chemokines that ensure the migration of monocytes/macrophages, NK cells and activated T-lymphocytes to the inflammation focus [20]; thus, the presence of this mechanism of anti-inflammatory action of prostatic peptides may be of great practical importance.

The high biological activity of Prostatilen is manifested in the ability to modulate metabolic processes. The experiment showed that administration of Prostatilen at a dose of 0.02 mg in 1 mL of saline solution to small laboratory animals every other day for three weeks resulted in a decrease in the levels of triglycerides, total cholesterol, and uric acid in the blood serum, and an increase in the levels of serotonin and catecholamines in the testes [21–23].

The immunotropic effect of Prostatilen, which manifests itself as a modulating and stimulating effect, is clinically very important [14, 15]. Prostatilen was found to promote an increase in the functional activity of T-lymphocytes, NK cells, and phagocytes [15, 24].

The prostatic peptides have a direct myotropic effect on the bladder smooth muscles. It has been revealed that Prostatilen *in vitro* increases the basal tone and contractile activity of the detrusor, and increases the amplitude of its phasic contractions [12, 16]. In this case, prostatic peptides cause a decrease in spontaneous contractile activity of the detrusor, which is possibly associated with the effect of peptides on the pacemaker bladder smooth muscle cells [16]. Thus, Prostatilen has a regulatory effect on the detrusor and enhances the reduced contractile activity and inhibits the increased one. This unique effect of Prostatilen is of great clinical significance.

Prostatilen has a number of important properties that are also inherent in other peptide bioregulators, one of which is a pronounced geroprotective effect. Studies have shown that the drug stimulates the growth of prostate cell cultures obtained from young and old animals, demonstrating high tissue specificity and selectivity of the molecular mechanism of action on the regeneration of prostate tissue during aging. Thus, Prostatilen has an inhibitory effect on involutional processes in the prostate gland, characteristic of premature aging and contributing to the development of age-related prostate pathology [25, 26].

Currently, several drugs belonging to the group of prostatic peptides are used for the treatment of urological disease, namely Vitaprost, Uroprost, and Samprost [27–30]; however, Prostatilen is the first prostatic peptide bioregulator that has been applied widely in medical practice. The year 2020 marks the 30th anniversary of its clinical use. In the early 1990s, the first clinical results were published, demonstrating high efficacy of Prostatilen in treatment of prostate diseases [31–33]. Subsequently, the drug has been used actively and successfully in treatment of other urological diseases [24, 34–36].

PROSTATILEN IN TREATMENT OF INFLAMMATORY DISEASES OF THE PROSTATE GLAND

Prostatic peptides are widely used to treat patients with chronic prostatitis. The high efficacy of Prostatilen in these patients is associated with the effect of the drug on the main pathogenetic mechanisms of prostatitis development. First of all, this relates to restoration of hemodynamics in the prostate gland, but the anti-inflammatory and immunotropic effects are also important. Microcirculatory disorders and congestive processes in the prostate gland are the most significant in development of chronic prostatitis [37–39]. Moreover, hemodynamic disorders are important not only in pathogenesis of chronic abacterial prostatitis (category III according to the NIH classification), but also in acute and chronic bacterial

prostatitis (categories I and II according to the NIH classification) [40]. The experiment has shown that inflammation of the prostate gland starts most often as aseptic; however, in almost a quarter of cases, the inflammatory process already in the acute phase proceeds as a bacterial one [17]. Bacterial prostatitis is probably caused by a decrease in the prostate gland resistance due to congestive disorders, causing, among other things, a decrease in the tone of the excretory prostatic ducts with urethro-prostatic refluxes, as well as deterioration in the bactericidal properties of the prostate secretion with subsequent infection. When studying the efficacy of Prostatilen on experimental models of acute and chronic prostatitis, it was revealed that administration of Prostatilen to animals at a dose of 0.1 mg/100 g of body weight for 5–10 days reduced leukocyte infiltration of the prostate tissue, improved the functional activity of the acini epithelium, and eliminated venule thrombosis. This effect was noted in both abacterial and bacterial prostatitis [17].

In 1991, the results of the first large-scale clinical study of Prostatilen efficacy in treating patients with chronic prostatitis, conducted under the guidance of Professor V.N. Tkachuk, were published. The study included 307 men aged 18 to 70 years, who received Prostatilen at a daily dose of 5 mg or 10 mg intramuscularly 10 days. Clinical improvement, expressed in a decrease or elimination of pain and dysuria, an improvement in sexual function, was registered in almost all patients, and in 55.4% of them it was persistent and was noted during all 6 months of the follow-up [31]. Among the 230 patients who complained of sexual dysfunction, 102 indicated complete recovery, and 96 noted an improvement. Subjective data were confirmed by the results of laboratory and instrumental studies. The normalization of the size and consistency of the prostate gland were noted, as well as a decrease in the leukocyte counts in urine, ejaculate, and prostate secretions, and an improvement in urination. Similar results were obtained by other researchers who registered clinical improvement in 95% of patients treated with Prostatilen [32, 33]. The efficacy revealed in the experiment and confirmed under clinical conditions made the prostate peptides one of the key drugs for treatment of patients with abacterial and bacterial prostatitis, both as a monotherapy and in combination with other drugs.

The study conducted at the Department of Urology of the First Pavlov Saint Petersburg State Medical University showed the high efficacy of the combined use of Prostatilen and a synthetic analog of the thymus peptide (Thymogen) in patients with chronic bacterial prostatitis [41]. Sixty-three patients monitored were distributed into three groups. Thymogen at a dose of 100 μg/day was prescribed to patients of group 1; Prostatilen in rectal suppositories of 30 mg daily was prescribed to patients of group 2; and a combination of Thymogen and Prostatilen in the above doses was prescribed to patients of group 3. The course of treatment was 5 days. At the same time, all patients received etiotropic treatment in accordance with the results of the antibiogram of the prostate exprimate. The greatest efficacy was noted with the combination treatment of peptide bioregulators of the prostate and thymus. The duration of the clinical effect preservation after the treatment in 75% of patients in group 2 exceeded 4 months. In 84% of patients in the group 3, it exceeded 5 months. The study results enabled the conclusion that the best clinical results with the combined use of Prostatilen and Thymogen in comparison with monotherapy with each of them are associated with a deeper effect on prostatitis pathogenesis and indicators of immunological homeostasis.

PROSTATILEN IN TREATMENT OF PATIENTS WITH REPRODUCTIVE FUNCTION DISORDERS

Inflammation of the prostate gland has an adverse effect on spermogram parameters and male fertility [42, 43]. The meta-analysis published by R.A. Condorelli et al [44] showed that in patients with chronic bacterial prostatitis, there is a tendency for a decrease in the concentration of spermatozoa, as well as a decrease in their viability, and general and progressive motility. In chronic abacterial

prostatitis and chronic pelvic pain syndrome, there is a tendency for a decrease in ejaculate volume, and in the concentration and progressive motility of spermatozoa, and a change in the spermatozoa morphology, as well as a decrease in the concentration of zinc in the ejaculate, and an increase in the amount of antisperm antibodies in it.

The effect of prostate peptides on the reproductive function of patients with chronic prostatitis was investigated in several clinical studies. The pathogenetic justification and clinical efficacy of Prostatilen were confirmed by the results of a study by S.A. Selkov et al [45], who monitored 32 patients with chronic prostatitis complicated by impaired erectile and reproductive functions. Patients in the control group received standard therapy, and patients in the main group received standard therapy with the addition of Prostatilen rectal suppositories two times a day for 10 days. After the treatment, the concentration of spermatozoa in patients receiving Prostatilen increased from 35.3 to 44.2 million/mL (+9%), and in the comparison group, it increased from 34.1 to 35.3 million/mL (+4%). Also, with the use of Prostatilen, a more pronounced positive dynamics of sperm motility indicators of categories A and B was noted. The number of morphologically normal forms increased in the Prostatilen group from 53% to 73% ($p < 0.05$), while in the comparison group it remained practically the same. In addition to the positive changes in spermogram indices in patients treated with Prostatilen, a more pronounced improvement in erectile function was revealed [45].

In order to increase the efficacy of treatment of patients with reproductive disorders, based on the previously registered drug Prostatilen (rectal suppositories, 30 mg, RU LS-000925 dated 05/31/2010), a special form of the drug, Prostatilen AC (rectal suppositories), was developed. In addition to regulatory peptides of the prostate gland, Prostatilen AC includes a composition of the substance of L-arginine (100 mg) and zinc (23 mg) in the form of a chelate compound of zinc arginyl glycinate (180 mg). The first results of experimental studies using Prostatilen AC demonstrated very encouraging results [46]. Small laboratory animals with induced chronic prostatitis received Prostatilen AC at a dose of 190 mg/kg of animal weight. The drug was administered 28 days after the initiation of inflammation for 30 days in molten form using an atraumatic probe. The study results revealed that Prostatilen AC had a pronounced organotropic anti-inflammatory effect, which manifested as a decrease in prostate weight, a decrease in protein level in urine, acid phosphatase activity, concentration of ceruloplasmin and C-reactive protein in blood serum.

The positive results of experimental studies have been confirmed under inpatient conditions. In a multicenter clinical study, 98 men aged 25–45 years with a verified diagnosis of chronic abacterial prostatitis and the presence of associated reproductive dysfunctions were followed-up [47]. Prescribing Prostatilen AC to patients resulted in a decrease in the level of antisperm antibodies in the ejaculate. By the end of the study, the proportion of patients with antisperm antibodies in the ejaculate decreased by 22.4%. The results of the study are of great practical importance, since an excessive level of antisperm antibodies in the ejaculate is a laboratory sign of autoimmune male infertility.

In another study, conducted at the Department of Urology, First Pavlov Saint Petersburg State Medical University, the influence of Prostatilen AC on the degree of sperm DNA fragmentation was analyzed [48]. This disorder is a special form of genetic damage to the DNA of the male gamete, which can lead to problems with fertility and embryonic development. The higher the number of lesions, the lower the genetic material integrity and the probability of pregnancy [49]. The study included 25 patients with chronic abacterial prostatitis, who sought medical help due to miscarriage at early term in a spouse (sexual partner). Patients received Prostatilen AC daily in the form of rectal suppositories, with 10 suppositories in a course, with a repeated course in 20 days. The degree of sperm DNA fragmentation averaged 18.99% ± 6.87% before treatment and 9.76% ± 4.32% after treatment. Damage

to the integrity of the sperm DNA reduces their fertilizing ability and represents one of the main reasons leading to the arrest of the development and elimination of the embryo at the early stages of embryogenesis, both in the natural reproductive cycle and during the implementation of procedures of assisted reproductive technologies. The results of the study led to the conclusion that when treating patients with chronic abacterial prostatitis, Prostatilen AC improves the fertile properties of the ejaculate, normalizes sperm DNA fragmentation, and can be recommended for preparation for medically assisted procreation procedures. The persistent positive effect of Prostatilen AC in this category of patients persisted for 2 months with a tendency to attenuation by the end of the month 3, which enabled to recommend repeated courses of treatment 2 months after the end of therapy [50]. The results of the study by O.B. Zhukov et al [51] confirmed that Prostatilen AC can be considered the drug of choice in the treatment of male infertility during the period of planned preparation of men for the use of assisted reproductive technologies. When the drug was administered, the concentration of spermatozoa in 1 mL increased by 32.5%, the number of normal morphological forms increased by 20%, and the proportion of spermatozoa with fast translation movement increased by 18% [51]. Another study by O.B. Zhukov et al [52] showed that administration of Prostatilen AC for 20 days to patients with chronic abacterial prostatitis and impaired reproductive function promotes an increase in the proportion of progressively mobile forms of spermatozoa by 62% compared with the initial level, and a decrease in the level of reactive oxygen species in the ejaculate and the proportion of spermatozoa with fragmented DNA. A decrease in the number of leukocytes in the ejaculate was also registered, which was associated by the authors with the anti-inflammatory effect of Prostatilen AC [52]. The clinical results obtained show that the use of Prostatilen in the treatment of patients with chronic prostatitis and pathospermia is pathogenetically substantiated and clinically effective.

PROSTATILEN IN TREATMENT OF BENIGN PROSTATE HYPERPLASIA

The treatment of patients with benign prostatic hyperplasia (BPH) is an important field of clinical use of Prostatilen. The link between BPH and chronic inflammation in the prostate gland (chronic prostatitis) has been proven in numerous studies: BPH is detected 2.4 times more often in patients who have previously been diagnosed with chronic prostatitis [53]. The mechanism of the effect of chronic inflammation on the development of BPH can be represented as follows: When inflammation occurs, infiltrates are formed in the prostate tissue, which consist mainly of T cells and macrophages. In these inflammatory infiltrates, cytokines (IL-2, IL-6, IL-8, IL-15 and gamma interferon) are produced, which enhance the proliferation of prostate cells, mostly fibroblasts. Prostate cells adjacent to the foci of inflammation die for unclear reasons, and their place is taken by stromal hyperplasia [54]. Proliferation of prostate epithelial cells is stimulated by a proinflammatory chemokine, MCP-1, the content of which increases in the prostate tissue and secretions in cases of hyperplasia [55]. This effect of inflammation on the proliferation of prostate tissue is associated with age-related weakening of the immune system. Along with hormonal imbalance, it contributes to damage to the population of suppressor cells, which leads to gradual infiltration of the prostate with lymphocytes and triggering a cascade of events resulting in BPH.

The pathogenetic grounds for the use of Prostatilen in patients with BPH is the anti-inflammatory, antiproliferative, and immunomodulatory effects of the drug. In addition, it has been suggested that prostatic peptides comprise substances that have an inhibitory effect on the chemokine MCP-1, which also inhibits the proliferation of prostate cells. The results of experimental studies of small laboratory animals with induced BPH were very indicative, as they revealed that Prostatilen at a dose of 1 mg/kg prevents an increase in the weight and volume of the prostate gland [56]. In this regard, the prescription of bioregulatory therapy with Prostatilen

to BPH patients seems to be pathogenetically reasonable. Clinical studies have shown the high efficacy of Prostatilen in treatment of BPH, which was reported in numerous publications [36, 57–60]. Small single doses of the drug (5–10 mg per injection or up to 30 mg per rectal suppository) in short courses lasting 5–15 days at intervals of 3–6 months are the most appropriate for BPH patients [59]. This is evidenced by the results of a study conducted in the urology clinic of the First Pavlov Saint Petersburg State Medical University. The study included 56 patients with BPH without signs of severe infravesicular obstruction or indication for surgical treatment. Prostatilen rectal suppositories containing 30 mg of the drug and 90 mg of Dimexidum, at a dose of one suppository at night for 15 days, were prescribed to all patients. Treatment courses were repeated every 3 months during one year, with a total of four courses. After the course 1 of treatment, all patients noted a decrease in the severity of dysuria. The frequency of urination decreased from 9.4 ± 1.4 to 5.3 ± 1.1 times a day ($p < 0.05$), the volume of residual urine in the bladder decreased by more than one and a half times, and the maximum urine flow rate increased from 7.9 ± 2.5 to 17.8 ± 1.7 mL/s ($p < 0.001$). Clinical improvement was confirmed by a significant decrease in the IPSS score (International Prostate Symptom Score). Clinical effects persisted after the treatment until the start of the next course of therapy. The intensity of regression of obstructive and irritative symptoms was more pronounced during course 1 of treatment, which was apparently associated with the suppression of active inflammation in the prostate gland at the start of therapy. After 1 year from the start of treatment, the patients under study had a significant increase in the maximum rate of urination and a decrease in the volume of residual urine compared with the initial values. During 1 year of follow-up, none of the patients had acute urinary retention, hematuria, or increased residual urine volume, and there was no need for surgery. The treatment was tolerated well, and there were no treatment-related adverse events [59]. The results of this and a number of other studies indicate that efficacy of Prostatilen in treatment of BPH patients is often not only not inferior, but also surpasses the results of a number of indicators of the main drugs for treatment of BPH, namely 5α-reductase inhibitors and alpha-blockers [60]. In the course of treatment, the severity of symptoms of the lower urinary tract decreases, the quality of life of patients increases, and the evacuation function of the bladder improves, as evidenced by an increase in the maximum urine flow rate and a decrease in the volume of residual urine.

Prostatilen is characterized by a direct myotropic effect on the detrusor, which has its own unique properties. The experiment has shown that with a decrease in the contractile activity of the bladder myocytes, Prostatilen has a stimulating effect, while in spontaneous activity (hyperactivity) of the detrusor, it promotes its inhibition [16, 34]. Such a multidirectional effect of the drug is associated with the fundamental biological property of regulatory peptides, namely the ability to exert a normalizing effect depending on the nature of pathological changes in the organ. This effect is of great clinical importance, since in BPH patients in the compensation stage, the detrusor contractile activity often increases, which is clinically manifested by overactive bladder, and with a decrease in the detrusor compensatory potential, its hypoactivity is revealed [61, 62]. In this regard, the results of the use of Prostatilen in BPH patients are very significant, as, on the one hand, it helps to reduce the severity of irritative symptoms, and on the other hand, it helps to improve the urine outflow from the bladder. This effect of prostatic peptides, in addition to the direct myotropic effect, was possibly caused by the influence on blood flow in the bladder. It has been revealed that with infravesicular obstruction, signs of bladder ischemia are noted, regardless of the stage of its functional compensation [62–65]. The use of Prostatilen helps to improve blood flow in the bladder wall, which is accompanied by a decrease in the severity of clinical symptoms.

The ability to exert a regulatory effect on detrusor myocytes is used in the prevention and treatment of disorders of urinary bladder evacuation function

after surgical interventions, manifested by acute urinary retention. Administration of Prostatilen prevented reflex urinary retention in operated patients or contributed to the restoration of independent urination in them, which was probably due to increased contractile activity of the detrusor [34, 66].

PROSTATILEN IN TREATMENT OF INFECTIOUS INFLAMMATORY DISEASES OF THE KIDNEYS AND BLADDER

The therapeutic capabilities of Prostatilen were also studied in the treatment of infectious and inflammatory diseases of the kidneys and urinary bladder. The clinical application of the drug was preceded by experimental confirmation of its efficacy. On a model of chronic pyelonephritis in small laboratory animals, the laboratory and morphological signs of chronic inflammation in the kidney disappeared or decreased sharply under the influence of Prostatilen at a dose of 0.1 mg per 100 g of body weight. The results of monotherapy with Prostatilen for experimental chronic pyelonephritis were not inferior to those in the use of etiotropic therapy [19]. Clinical studies demonstrated that inclusion of Prostatilen in the complex therapy of patients with chronic pyelonephritis in the phase of latent inflammation at a dose of 5 mg intramuscularly daily for 5 days contributed to a decrease in the inflammatory process activity in the kidney, including in patients in whom previous antibiotic therapy did not lead to positive results. When Prostatilen was prescribed to patients with chronic pyelonephritis, hemocoagulation indicators normalized, blood fibrinolytic activity increased, and its rheological properties improved, which contributed to the restoration of microcirculation in the kidney [19, 24]. The immunotropic effect of Prostatilen was expressed with an increase in the number of lymphocytes with the phenotype $CD3^+$ and $CD2^+DR^+$; an increase in the RILM with ConA (reaction of inhibition of lymphocyte migration with concanavalin A), indicating an increase in the functional activity of T-lymphocytes; and an increase in the content and normalization of the ratio of B-lymphocyte subpopulations. An important indicator of the immunomodulatory effect of Prostatilen was the change in the $CD4^+/CD8^+$ ratio. The value of the indicator, which reduced in patients with primary pyelonephritis to 1.02 ± 0.11 after the course of treatment, reached 1.52 ± 0.21 ($p < 0.05$). In patients with secondary pyelonephritis, the $CD4^+/CD8^+$ ratio increased from 1.06 ± 0.12 to 1.39 ± 0.18 ($p < 0.05$) [24]. A significant increase in the values of the NBT test (induced test of nitroblue tetrazolium recovery) revealed Prostatilen's ability to enhance the metabolic activity of phagocytes, which indicated its ability to increase the functional activity and reserve capabilities of oxygen-dependent enzyme systems of phagocytes [15]. Thus, the therapeutic effect of Prostatilen in patients with chronic pyelonephritis is mainly due to an improvement in renal blood flow and the presence of a significant immunotropic effect. These data were reason for recommending the inclusion of Prostatilen in the complex therapy of patients with chronic pyelonephritis in preparation for elective surgical interventions, including extracorporeal lithotripsy [19, 24].

The use of an experimental model of acute cystitis in small laboratory animals showed a distinct anti-inflammatory effect of Prostatilen [35]. The drug was administered at a dose of 0.1 mg per 100 g of animal body weight once a day for 10 days. Treatment with Prostatilen in the experiment gave a result comparable in laboratory and morphological parameters with those in treatment with an antibacterial drug. Under clinical settings, the efficacy of Prostatilen was studied in the treatment of women with uncomplicated acute cystitis, who received it as one intravaginal suppository at night for 5 days. The results of Prostatilen therapy were not inferior to the results of the use of antibacterial drugs. The possibility of abandoning antibiotics was previously demonstrated in a study of the use of herbal medicinal products [67] and seems to be very important, especially in relation to the tendency of increased antibacterial drug resistance among uropathogens. The therapeutic effect of Prostatilen in the treatment of cystitis is based on the anti-inflammatory effect and the ability to improve

microcirculation in the bladder wall, which is significantly affected in such patients [35, 68].

ASPECTS OF PRODUCTION TECHNOLOGY AND DOSAGE FORMS OF PROSTATILEN

The results of clinical studies confirm the high efficacy and pathogenetic justification of the use of Prostatilen in treatment of urological patients. From a treatment safety standpoint, it is very important that, despite their high biological activity, peptides of the prostate gland do not have any side effects on the structure and functions of the body organs and systems and do not have a mutagenic effect [69].

The efficacy and safety of the clinical use of Prostatilen is directly related to the aspects of its production. The production technology of Prostatilen includes the principle of sequential filtration of the initial biological fraction with a micron rating of 13 kDa for the final filter. This enables the exclusion of peptides with molecular weights above this value. The absence of high molecular weight compounds in Prostatilen composition contributes to good treatment tolerability. This is associated with both a decrease in the risk of allergic reactions when using a peptide fraction with a low molecular weight, and with ensuring prion safety. Molecular weight of the normal form of prion protein is known to be 33–35 kDa, and that of the pathogenic form is 27–30 kDa [70]. Despite the fact that the prostate tissue is classified as "tissues with no risk of prion contamination" (category IC), the risk of contamination of raw materials cannot be completely ruled out; therefore filtration is an additional measure to ensure safety and prevent the development of prion diseases.

The low molecular weight of the peptide fractions included in Prostatilen increases the bioavailability of transrectal dosage forms of the drug, which increases its clinical efficacy. There are several obstacles when using rectal suppositories for the drug absorption, namely the apical membrane, the cell body, and tight intercellular contacts. The ability to overcome these barriers is determined by the fractionation factor; that is, the ratio of the substance concentration in two phases, charge, hydro- and lipophilicity of the molecule, the ability to form hydrogen bonds, and also molecular weight [71]. The lower the fractionation factor and the higher the molecular weight, the worse is the substance absorption. The presence of charge and the ability to form hydrogen bonds also reduce the drug absorption [72]. The hydrophilicity of peptides affects negatively their penetrating ability and bioavailability [73]. It has been demonstrated, particularly, that only small molecules (less than 0.075–0.100 kDa) can diffuse rapidly enough through mucosal cells [73], in contrast to peptides, even those small in size. This is due to the fact that absorption of substances in the rectal mucosa is possible only by transcellular or paracellular routes using passive transport through the cell itself or through the intercellular spaces. In an adult, active transport and pinocytic absorption, as well as peptidase activity in this part of the gastrointestinal tract, are minimal or absent [74]. The hydrophilic nature of peptides and the size of their molecules prevent them from penetration into enterocytes without the use of excipients. Therefore, in order to improve bioavailability, so-called enhancers are used which enhance the permeability of cells of the rectal mucosa, which improves the rate of fluidity of cell membranes, increases the size of the intercellular space, reduces the viscosity of the mucus layer adjacent to the rectal mucosa, and increases water penetration [72]. Dimexidum functions as an enhancer in the Prostatilen rectal suppositories, which enhances penetration by increasing the permeability of cell membranes [75].

Thus, the production technology of the drug Prostatilen provides it with important advantages in terms of bioavailability. These advantages are due to two important factors. Firstly, the presence of Dimexidum in the composition of Prostatilen 30 mg and 50 mg suppositories, which functions as an enhancer to intensify the penetration of prostatic peptides through the intestinal wall. In addition, Dimexidum itself has an anti-inflammatory effect. Secondly, the increase in clinical efficiency of

Prostatilen is contributed by the fact that it consists of a low molecular weight protein-peptide fraction of biologically active regulatory proteins, rather than large physiologically inactive proteins of connective tissue and cell membranes. The composition of rectal suppositories Prostatilen AC, in addition to prostatic peptides, comprises substances (zinc and arginine) that influence male reproductive function.

CONCLUSION

The results of numerous experimental and clinical studies confirm the pathogenetic justification of the use of Prostatilen in treatment of urological patients. The drug production technology provides a peptide low molecular weight active substance, which ensures high bioavailability, efficacy, and safety of its use.

REFERENCES

1. Фармакопея России. Pharmacoroea Rossica. – СПб.: Альфарет, 2017. – 158с. [Farmakopeya Rossii. Pharmacoroea Rossica. Saint Petersburg: Al'faret, 2017. 158 p. (In Russ.)].
2. Prokopov IA, Kovaleva EL, Minaeva ED, et al. Animal-derived medicinal products in Russia: Current nomenclature and specific aspects of quality control. *J Ethnopharmacol*. 2019;240:111933. https://doi.org/10.1016/j.jep.2019.111933.
3. Морозов В.Г., Хавинсон В.Х. Новый класс биологических регуляторов многоклеточных систем — цитомедины // Успехи современной биологии. – 1983. – Т. 96. – № 3. – С. 339–352. [Morozov VG, Khavinson VKh. Novyy klass biologicheskikh regulyatorov mnogokletochnykh sistem – tsitomediny. *Usp Sovrem Biol*. 1983;96(3):339-352. (In Russ.)]
4. Морозов В.Г., Хавинсон В.Х., Кожемякин А.Л. Цитомедины // Вопросы медицинской химии. – 1982. – Т. 28. – № 4. – С. 114–118. [Morozov VG, Khavinson VKh, Kozhemyakin AL. Tsitomediny. *Vopr Med Khim*. 1982;28(4):114-118. (In Russ.)]
5. Ашмарин И.П. Малые пептиды в норме и при патологии // Патологическая физиология и экспериментальная терапия. – 1982. – Т. 26. – № 4. – С. 13–27. [Ashmarin IP. Malye peptidy v norme i pri patologii. *Patol Fiziol Eksp Ter*. 1982;26(4):13-27. (In Russ.)]
6. Кузник Б.И., Морозов В.Г., Хавинсон В.Х. Цитомедины и их роль в регуляции физиологических функций // Успехи современной биологии. – 1995. – Т. 115. – № 3. – С. 353–367. [Kuznik BI, Morozov VG, Khavinson VKh. Tsitomediny i ikh rol' v regulyatsii fiziologicheskikh funktsiy. *Usp Sovrem Biol*. 1995;115(3):353-367. (In Russ.)]
7. Хавинсон В.Х., Кветной И.М., Ашмарин И.П. Пептидергическая регуляция гомеостаза // Успехи современной биологии. – 2002. – Т. 122. – № 2. – С. 190–192. [Khavinson VKh, Kvetnoy IM, Ashmarin IP. Peptidergicheskaya regulyatsiya gomeostaza. *Usp Sovrem Biol*. 2002;122(2):190-192. (In Russ.)]
8. Федореева Л.И, Киреев И.И., Хавинсон В.Х., Ванюшин Б.Ф. Проникновение коротких флуоресцентно-меченых пептидов в ядро в клетках HeLa и специфическое взаимодействие пептидов с дезоксирибоолигонуклеотидами и ДНК *in vitro* // Биохимия. – 2011. – Т. 76. – № 11. – С. 1505–1516. [Fedoreeva LI, Kireev II, Havinson VH, Vanjushin BF. Penetration of short fluorescence-labeled peptides into the nucleus in HELA cells and *in vitro* specific interaction of the peptides with deoxyribooligonucleotides and DNA. *Biokhimiia.* 2011;76(11):1505-1516. (In Russ.)]. https://doi.org/0.1134/S0006297911110022.
9. Хавинсон В.Х., Анисимов В.Н. 35-летний опыт исследований пептидной регуляции старения // Успехи геронтологии. – 2009. – Т. 22. – № 1. – С. 11–23 [Havinson VKh, Anisimov VN. 35-year experience in study of peptide regulation of aging. *Adv Gerontol.* 2009;22(1):11-23. (In Russ.)]
10. Хавинсон В.Х., Морозов В.Г., Кузник Б.И., и др. Влияние полипептидов предстательной железы на систему гемостаза // Фармакология и токсикология. – 1985. – Т. 48. – № 5. – С. 69–71. [Khavinson VKh, Morozov VG, Kuznik BI, et al. Effect of polypeptides from the prostate on the hemostasis system. *Farmakol Toksikol*. 1985;48(5):69-71. (In Russ.)]
11. Петрищев Н.Н., Михайлова Н.А., Горбачев А.Г., и др. Влияние комплекса полипептидов, выделенных из предстательной железы животных, на тромбообразование // Патологическая физиология и экспериментальная терапия. – 1991. – Т. 35. – № 4. – С. 5–6. [Petrishchev NN, Mikhaylova NA, Gorbachev AG, et al. Vliyanie kompleksa polipeptidov, vydelennykh iz predstatel'noy zhelezy zhivotnykh, na tromboobrazovanie. *Patol Fiziol Eksp Ter*. 1991;35(4):5-6. (In Russ.)]
12. Аль-Шукри С.Х., Горбачев А.Г., Кузьмин И.В., Хавинсон В.Х. Введение в биорегулирующую терапию при урологических болезнях. – СПб.: Наука, 1996. – 93 с. [Al'-Shukri SKh, Gorbachev AG, Kuz'min IV, Khavinson VKh. Vvedenie v bioreguliruyushchuyu terapiyu pri urologicheskikh boleznyakh. Saint Petersburg: Nauka; 1996. 93 p. (In Russ.)]
13. Юшков В.В., Хавинсон В.Х. Выявление и анализ противовоспалительной активности иммуномодуляторов // Патологическая физиология и экспериментальная терапия. – 1993. – Т. 37. – № 2. – С. 11–13. [Yushkov VV, Khavinson VKh. Vyyavlenie i analiz protivovospalitel'noy aktivnosti immunomodulyatorov. *Patol Fiziol Eksp Ter*. 1993;37(2):11-13. (In Russ.)]
14. Горбачев А.Г., Напалков П.Н., Тотолян А.А., Хавинсон В.Х. Влияние полипептидного препарата из предстательной железы (простатилен) на показатели иммунного статуса больных хроническим простатитом / Сб. тезисов IV Всесоюзного

съезда урологов; Москва, 10–12 октября 1990 г. – М.,1990. С. 261–262. [Gorbachev AG, Napalkov PN, Totolyan AA, Khavinson VK. Vliyanie polipeptidnogo preparata iz predstatel'noyzhelezy (prostatilen) na pokazateli immunnogo statusa bol'nykh khronicheskim prostatitom. In: Proceedings of the 4th All-Union Congress of urologists; Moscow, 10-12 Oct 1990. Moscow; 1990. P. 261-262. (In Russ.)]

15. Аль-Шукри С.Х., Горбачев А.Г., Кузьмин И.В. Влияние простатилена на метаболическую активность фагоцитов у больных хроническим пиелонефритом // Казанский медицинский журнал. – 1996. – Т. 77. – № 3. – С. 200–201. [Al'-Shukri SKh, Gorbachev AG, Kuz'min IV. Vliyanie prostatilena na metabolicheskuyu aktivnost' fagotsitov u bol'nykh khronicheskim pielonefritom. *Kazan Med Zh*. 1996;77(3):200-201. (In Russ.)]
16. Барабанова В.В., Горбачев А.Г., Парастаева М.М., Хавинсон В.Х. Влияние пептидов предстательной железы на сократительную активность гладкомышечных клеток мочевого пузыря // Физиологический журнал имени И.М. Сеченова. – 1993. – Т. 79. – № 2. – С. 90–96. [Barabanova VV, Gorbachev AG, Parastaeva MM, KhavinsonVKh. Vliyanie peptidov predstatel'noy zhelezy na sokratitel'nuyu aktivnost' gladkomyshechnykh kletok mochevogo puzyrya. *Fiziol Zh Im I M Sechenova*. 1993;79(2): 90-96. (In Russ.)]
17. Горбачев А.Г., Тюрин А.Г. Лечение острого и хронического простатита пептидным препаратом из предстательной железы в эксперименте // Урологические ведомости. – 2015. – Т. 5. – № 4. – С. 20–26. [Gorbachev AG, Tyurin AG. The treatment of acute and chronic prostatitis in experiment by peptides of the prostate gland. *Urologicheskie vedomosti.* 2015;5(4): 20-26. (In Russ.)]. https://journals.eco-vector.com/uroved/article/view/2879.
18. Аль-Шукри С.Х., Петрищев Н.Н., Горбачев А.Г. Влияние простатилена на показатели гемостаза при хроническом простатите (клинико-экспериментальное исследование) // Урология и нефрология. – 1997. – № 3. – С. 38–41. [Al'-Shukri SKh, Petrishchev NN, Gorbachev AG. Vliyanie prostatilena na pokazateli gemostaza pri khronicheskom prostatite (kliniko-eksperimental'noe issledovanie). *Urol Nefrol (Mosk)*. 1997;(3):38-41. (In Russ.)]
19. Кузьмин И.В. Простатилен в лечении хронического пиелонефрита (экспериментально-клиническое исследование): Автореф. дис. … канд. мед. наук. – СПб., 1996. [Kuz'min IV. Prostatilen v lechenii khronicheskogo pielonefrita (eksperimental'no-klinicheskoe issledovanie). [dissertation] Saint Petersburg; 1996. (In Russ.)]
20. Mukaida N. Interleukin-8 (IL-8) and monocyte chemotactic and activating factor (MCAF/MCP-1), chemokines essentially involved in inflammatory and immune reactions. *Cytokine Growth Factor Rev*. 1998;9(1):9-23. https://doi.org/10.1016/s1359-6101(97)00022-1.
21. Кляшева Р.И., Сергеева В.Е., Клочкова Е.А. Влияние простатилена на содержание триглицеридов в сыворотке крови и катехоламинов в семенниках крыс // Актуальные направления научных исследований XXI века: теория и практика. – 2013. – № 3. – С. 45–50. [Klyasheva RI, Cergeeva VE, Klochkova EA. Vliyanie prostatilena na soderzhanie triglitseridov v syvorotke krovi i katekholaminov v semennikakh krys. *Aktual'nye napravleniya nauchnykh issledovaniy XXI veka: teoriya i praktika*. 2013;(3): 45-50. (In Russ.)]
22. Кляшева Р.И., Сергеева В.Е., Клочкова Е.А. Исследование влияния простатилена на содержание общего холестерола в сыворотке крови и серотонина в семенниках // Вестник Чувашского университета. – 2014. – № 2. – С. 266–269. [Klyasheva RI, Sergeeva VE, Klochkova EA. Investigation influence of prostatilen on the content of total cholesterol in serum and serotonin rat testis. *Vestnik Chuvashskogo universiteta*. 2014;(2):266-269. (In Russ.)]
23. Кляшева Р.И., Сергеева В.Е., Клочкова Е.А. Исследование влияния простатилена на содержание мочевой кислоты в сыворотке крови и гистамина в семенниках крыс // Acta Medica Eurasica. – 2015. – № 1. – С. 1–5. [Kljasheva RI, Cergeeva VE, Klochkova EA. Studying prostatilen's influence on the content of uric acid in blood serum and gistamin in rat's testes. *Acta Medica Eurasica*. 2015;(1):1-5. (In Russ.)]
24. Аль-Шукри С.Х., Горбачев А.Г., Кузьмин И.В. Биорегулирующая терапия больных хроническим пиелонефритом // Урология и нефрология. – 1997. – № 4. – С. 6–8. [Al'-Shukri SKh, Gorbachev AG, Kuz'min IV. Bioreguliruyushchaya terapiya bol'nykh khronicheskim pielonefritom. *Urol Nefrol (Mosk)*. 1997;(4):6-8. (In Russ.)]
25. Хавинсон В.Х., Кузник Б.И., Рыжак Г.А. Пептидные биорегуляторы — новый класс геропротекторов. Сообщение 1. Результаты экспериментальных исследований // Успехи геронтологии. – 2012. – Т. 25. – № 4. – С. 696–708. [Khavinson VKh, Kuznik BI, Ryzhak GA. Peptide bioregulators: the new class of geroprotectors. Message 1. Experimental studies results. *Adv Gerontol*. 2012;25(4):696-708. (In Russ.)]
26. Рыжак А.П., Чалисова Н.И., Линькова Н.С., и др. Влияние полипептидов на регенерацию клеток в культуре разных тканей молодых и старых крыс // Успехи геронтологии. – 2015. – Т. 28. – № 1. – С. 97–103. [Ryzhak AP, Chalisova NI, Lin'kova NS, et al. Polypeptides influence on tissue cell cultures regeneration of various age rats. *Adv Gerontol.* 2015;28(1):97-103. (In Russ.)]
27. Аль-Шукри С.Х., Кузьмин И.В., Лукина Е.Е. Применение комплекса пептидов предстательной железы уропрост у больных с нарушением оттока мочи из мочевого пузыря // Экспериментальная и клиническая урология. – 2010. – № 3. – С. 80–84. [Al'-Shukri SKh, Kuz'min IV, Lukina EE. Uroprost peptide complex in treatment of patients with voiding disturbances. *Experimental & clinical urology*. 2010;(3):80-84. (In Russ.)]

28. Учваткин Г.В., Татаринцева М.Б. Простатические пептиды в лечении заболеваний предстательной железы // Урологические ведомости. – 2017. – Т. 7. – № 3. – С. 44–48. [Uchvatkin GV, Tatarintseva MB. The use of prostatic peptides in the treatment of prostate diseases. *Urologicheskie vedomosti.* 2017;7(3):44-48. (In Russ.)]. https://doi.org/10.17816/uroved7344-48.
29. Кузьмин И.В., Шабудина Н.О., Аль-Шукри С.Х. Пептиды предстательной железы в лечении больных с симптомами нижних мочевых путей вследствие доброкачественной гиперплазии предстательной железы // Эффективная фармакотерапия. – 2015. – № 18. – С. 16–22. [Kuz'min IV, Shabudina NO, Al'-Shukri SKh. Prostatic peptides in treatment of patients with lower urinary tract symptoms related to benign prostatic hyperplasia. *Effektivnaya farmakoterapiya*. 2015;(18):16-22. (In Russ.)]
30. Кузьмин И.В. Витапрост-форте в лечении больных доброкачественной гиперплазией предстательной железы: патогенетические основы и клинические результаты // Урология. – 2019. – № 4. – С. 141–147. [Kuz'min IV. Vitaprost forte in the treatment of patients with benign prostatic hyperplasia: pathogenetic basics and clinical results. *Urologiia.* 2019;(4):141-147. (In Russ.)]. https://doi.org/10.18565/urology.2019.4.141-147.
31. Ткачук В.Н., Горбачев А.Г., Хавинсон В.Х. Применение простатилена при лечении больных хроническим простатитом // Урология и нефрология. – 1991. – № 6. – С. 40–43. [Tkachuk VN, Gorbachev AG, Khavinson VKh. Primenenie prostatilena pri lechenii bol'nykh khronicheskim prostatitom. *Urol Nefrol (Mosk)*. 1991;(6):40-43. (In Russ.)]
32. Возианов А.Ф., Горпинченко И.И., Бойко Н.И., и др. Применение простатилена при лечении больных с заболеваниями предстательной железы // Урология и нефрология. – 1991. – № 6. – С. 43–46. [Vozianov AF, Gorpinchenko II, Boyko NI, et al. Primenenie prostatilena pri lechenii bol'nykh s zabolevaniyami predstatel'noy zhelezy. *Urol Nefrol (Mosk)*. 1991;(6):43-46. (In Russ.)].
33. Борисенко К.К., Хилинский М.М., Малышев А.М., Медведева И.И. Опыт применения простатилена в терапии хронического простатита // Вестник дерматологии и венерологии. – 1991. – № 8. – С. 47–50. [Borisenko KK, Khilinskiy MM, Malyshev AM, Medvedeva II. Opyt primeneniya prostatilena v terapii khronicheskogo prostatita. *Vestn Dermatol Venerol*. 1991;(8):47-50. (In Russ.)]
34. Аль-Шукри С.Х., Горбачев А.Г., Айвазян И.А., и др. Влияние простатилена на функциональную активность гладкомышечных органов у хирургических больных (клинико-экспериментальное исследование) // Хирургия. Журнал имени Н.И. Пирогова. – 1999. – № 1. – С. 47–49. [Al'-Shukri SK, Gorbachev AG, Ayvazyan IA, et al. Vliyanie prostatilena na funktsional'nuyu aktivnost' gladkomyshechnykh organov u khirurgicheskikh bol'nykh (kliniko-eksperimental'noe issledovanie). *Khirurgiia (Mosk)*. 1999;(1):47-49. (In Russ.)]
35. Аль-Шукри С.Х., Горбачев А.Г., Боровец С.Ю. Эффективность простатилена при остром цистите (экспериментально-клиническое исследование) // Нефрология. – 2009. – Т. 13. – № 2. – С. 92–95. [Al-Shukri SH, Gorbachev AG, Borovets SY. The effectiveness of prostatilen in acute cystitis (clinical and experimental investigation). *Nephrology.* 2009;13(2):92-95. (In Russ.)]. https://doi.org/10.24884/1561-6274-2009-13-2-92-95.
36. Аль-Шукри С.Х., Бобков Ю.А., Горбачев А.Г., и др. Наш опыт применения простатилена в урологии // Урология. – 2003. – № 6. – С. 32–36. [Al'-Shukri SKh, Bobkov YuA, Gorbachev AG, et al. Use of prostatilen in urology. *Urologiia*. 2003;(6):32-36. (In Russ.)]
37. Коган М.И., Белоусов И.И., Болоцков А.С. Артериальный кровоток в простате при синдроме хронической тазовой боли/хроническом простатите // Урология. – 2011. – № 3. – С. 22–28. [Kogan MI, Belousov II, Bolotskov AS. Arterial blood flow in the prostate in the syndrome of chronic pelvic pain / chronic prostatitis. *Urologiia.* 2011;(3):22-28. (In Russ.)]
38. Цуканов А.Ю., Ляшев Р.В. Нарушение венозного кровотока как причина хронического абактериального простатита (синдрома хронической тазовой боли) // Урология. – 2014. – № 4. – С. 33–38. [Tsukanov AY, Lyashev RV. Disorders of venous blood flow as a cause of chronic abacterial prostatitis (chronic pelvic pain syndrome). *Urologiia.* 2014;(4):37-42. (In Russ.)]
39. Крупин В.Н., Крупин А.В., Белова А.Н., Нашивочникова Н.А. Состояние гемодинамики предстательной железы у больных с миофасциальным болевым синдромом // Урологические ведомости. – 2017. – Т. 7. – № 4. – С. 39–43. [Krupin VN, Krupin AV, Belova AN, Nashivochnikova NA. The state of prostate hemodynamics in patients with myophascial pain syndrome. *Urologicheskie vedomosti.* 2017;7(4):39-43. (In Russ.)]. https://doi.org/10.17816/uroved7439-43.
40. Крупин В.Н., Крупин А.В., Нашивочникова Н.А. Оценка кровотока в предстательной железе у больных хроническим бактериальным простатитом // Урологические ведомости. – 2017. – Т. 7. – № 3. – С. 38–43. [Krupin VN, Krupin AV, Nashivochnikova NA. Evaluation of blood flow in prostate in patients with chronic bacterial prostatitis. *Urologicheskie vedomosti.* 2017;(3):38-43. (In Russ.)]. https://doi.org/10.17816/uroved7338-43.
41. Горбачев А.Г., Боровец С.Ю., Аль-Шукри С.Х., Рыбалов М.А. Эффективность сочетанной биорегулирующей терапии (простатилен и тимоген) у больных с инфекционным хроническим простатитом // Нефрология. – 2015. – Т. 19. – № 6. – С. 49–52. [Gorbachev AG, Borovets SYu, Al'-Shukri SKh, Rybalov MA. The efficacy of combined bioregulatory treatment (prostatilen + timogen) in patients with infectious chronic prostatitis. *Nephrology.* 2015;19(6):49-52. (In Russ.)]
42. Verze P, Cai T, Lorenzetti S. The role of the prostate in male fertility, health and disease. *Nat Rev Urol*. 2016;13(7):379-386. https://doi.org/10.1038/nrurol.2016.89.

43. Аль-Шукри С.Х., Кузьмин И.В., Слесаревская М.Н., Соколов А.В. Влияние низкоинтенсивного лазерного излучения на показатели эякулята у больных хроническим простатитом // Урологические ведомости. – 2015. – Т. 5. – № 4. – С. 8–12. [Al'-Shukri SKh, Kuz'min IV, Slesarevskaya MN, Sokolov AV. The effect of low-intensity laser radiation on semen parameters in patients with chronic prostatitis. *Urologicheskie vedomosti.* 2015;5(4):8-12. (In Russ.)]. https://doi.org/10.17816/uroved548-12.
44. Condorelli RA, Russo GI, Calogero AE, et al. Chronic prostatitis and its detrimental impact on sperm parameters: a systematic review and meta-analysis. *J Endocrinol Invest*. 2017;40(11):1209-1218. https://doi.org/10.1007/s40618-017-0684-0.
45. Сельков С.А., Петленко С.В., Селькова М.С. Применение препарата простатилен в комплексной терапии хронического простатита, ассоциированного с половыми и репродуктивными нарушениями // Андрология и генитальная хирургия. – 2012. – Т. 13. – № 3. – С. 93–96. [Sel'kov SA, Petlenko SV, Sel'kova MS. Use of prostatilene in the combination therapy of chronic prostatitis associated with sexual and reproductive disorders. *Andrology and genital surgery journal*. 2012;13(3):93-96. (In Russ.)]
46. Саватеева-Любимова Т.Н., Сивак К.В., Малинин В.В. Влияние суппозиториев Простатилен АЦ на течение экспериментального простатита // Урология. – 2012. – № 4. – С. 50–54. [Savateeva-Lyubimova TN, Sivak KV, Malinin VV. Effect of Prostatilen® AC suppositories on course of experimental prostatitis. *Urologiia.* 2012;(4):50-54. (In Russ.)]
47. Аль-Шукри С.Х., Петленко С.В., Боровец С.Ю., и др. Влияние препаратов Простатилен® АЦ и Простатилен® на уровень антиспермальных антител в эякуляте при лечении пациентов с хроническим абактериальным простатитом и сопутствующими нарушениями репродуктивной функции // Андрология и генитальная хирургия. – 2016. – Т. 17. – № 1. – С. 38–41. [Al'-Shukri SKh, Petlenko SV, Borovets SYu, et al. Effect of Prostatilene® AC and Prostatilene® on the ejaculate level of antisperm antibodies in the treatment of patients with chronic abacterial prostatitis and concomitant reproductive dysfunctions. *Andrology and genital surgery journal*. 2016;17(1):38-41. (In Russ.)]. https://doi.org/10.17650/2070-9781-2016-17-1-40-43.
48. Боровец С.Ю., Рыбалов М.А., Горбачев А.Г., Аль-Шукри С.Х. Влияние препарата Простатилен® АЦ на фрагментацию ДНК сперматозоидов при лечении пациентов с хроническим абактериальным простатитом и сопутствующими нарушениями репродуктивной функции // Андрология и генитальная хирургия. – 2017. – Т. 18. – № 3. – С. 54–58. [Borovets SYu, Rybalov MA, Gorbachev AG, Al'-Shukri SKh. Effect of Prostatilen AC on sperm DNA fragmentation in treatment of patients with chronic nonbacterial prostatitis and concomitant reproductive disorders. *Andrology and genital surgery journal*. 2017;18(3):54-58.(InRuss.)].https://doi.org/10.17650/2070-9781-2017-18-3-54-58.
49. Боровец С.Ю., Егорова В.А., Гзгзян А.М., Аль-Шукри С.Х. Фрагментация ДНК сперматозоидов: клиническая значимость, причины, методы оценки и коррекции // Урологические ведомости. – 2020. – Т. 10. – № 2. – С. 173–180. [Borovets SYu, Egorova VA, Gzgzyan AM, Al'-Shukri SKh. Fragmentation of sperm DNA: clinical significance, reasons, methods of evaluation and correction. *Urology reports (St. Petersburg).* 2020;10(2):173-180. (In Russ.)]. https://doi.org/10.17816/uroved102173-180.
50. Боровец С.Ю., Рыбалов М.А., Горбачев А.Г., и др. Отдаленные результаты лечения препаратом Простатилен® АЦ больных хроническим абактериальным простатитом с повышенной степенью фрагментации ДНК сперматозоидов // Андрология и генитальная хирургия. – 2018. – Т. 19. – № 2. – С. 52–57. [Borovets SYu, Rybalov MA, Gorbachev AG, et al. Long-term results of treatment of patients with chronic nonbacterial prostatitis and increased level of sperm DNA fragmentation with the Prostatilen® AC drug. *Andrology and genital surgery journal*. 2018;19(2):52-57. (In Russ.)]. https://doi.org/10.17650/2070-9781-2018-19-2-52-57.
51. Жуков О.Б., Евдокимов В.В., Брагина Е.Е. Улучшение качества жизни и морфофункциональных характеристик сперматозоидов у мужчин с хроническим абактериальным простатитом и программы прегравидарной подготовки к отцовству // Андрология и генитальная хирургия. – 2017. – Т. 18. – № 1. – С. 102–108. [Zhukov OB, Evdokimov VV, Bragina EE. Improvement of life quality and morphofunctional characteristics of spermatozoa in men with chronic nonbacterial prostatitis and programs of preconception preparation to fatherhood. *Andrology and genital surgery journal*. 2017;18(1):102-108. (In Russ.)]. https://doi.org/10.17650/2070-9781-2017-18-1-102-108.
52. Жуков О.Б., Брагина Е.Е., Левина А.В., и др. Сравнение эффективности препаратов, содержащих комбинацию аргинина и цинка, в лечении мужского бесплодия // Андрология и генитальная хирургия. – 2020. – Т. 21. – № 2. – С. 26–35. [Zhukov OB, Bragina EE, Levina AV, et al. Comparison of the effectiveness of medications containing a combination of zinc and arginine for treatment of male infertility. *Andrology and genital surgery journal*. 2020;21(2):26-35. (In Russ.)]. https://doi.org/10.17650/2070-9781-2020-21-2-26-35.
53. St Sauver JL, Jacobson DJ, McGree ME, et al. Longitudinal association between prostatitis and development of benign prostatic hyperplasia. *Urology*. 2008;71(3):475-479; discussion 479. https://doi.org/10.1016/j.urology.2007.11.155.
54. Kramer G, Marberger M. Could Inflammation be a key component in the progession of benign prostatic hyperplasia? *Curr Opin Urol*. 2006;16(1):25-29.
55. Fujita K, Ewing CM, Getzenberg RH, et al. Monocyte chemotactic protein-1 (MCP-1/CCL2) is associated with prostatic

growth dysregulation and benign prostatic hyperplasia. *Prostate*. 2010;70(5):473-481. https://doi.org/10.1002/pros.21081.

56. Белостоцкая Л.И., Никитченко Ю.В., Гомон О.Н., и др. Влияние биологически активных веществ животного и растительного происхождения на прооксидантно-антиоксидантный баланс при экспериментальной гиперплазии предстательной железы у крыс // Экспериментальная и клиническая фармакология. – 2006. – Т. 69. – № 4. – С. 66–68. [Belostotskaya LI, Nikitchenko YV, Gomon ON, et al. Influence of biologically active substances of animal and plant origin on prooxidant – antioxidant balance in rats with experimental prostatic hyperplasia. *Eksp Klin Farmakol.* 2006;69(4):66-68. (In Russ.)]. https://doi.org/10.30906/0869-2092-2006-69-4-66-68.
57. Аль-Шукри С.Х., Горбачев А.Г., Боровец С.Ю., и др. Лечение больных аденомой предстательной железы простатиленом // Урология. – 2006. – № 6. – С. 22–25. [Al'-Shukri SKh, Gorbachev AG, Borovets SYu, et al. Prostatilen treatment of prostatic adenoma. *Urologiia.* 2006;(6):22-25. (In Russ.)]
58. Аль-Шукри С.Х., Горбачев А.Г., Боровец С.Ю., и др. Влияние простатилена на расстройства мочеиспускания у больных доброкачественной гиперплазией предстательной железы // Урология. – 2005. – № 5. – С. 25–26. [Al'-Shukri SKh, Gorbachev AG, Borovets SYu, et al. Prostatilen effects on voiding disorders in patients with benign prostatic hyperplasia. *Urologiia.* 2005;(5):25-26. (In Russ.)]
59. Боровец С.Ю., Горбачев А.Г., Аль-Шукри С.Х., Рыбалов М.А. К патогенетическому обоснованию курсового лечения пептидными биорегуляторами больных с доброкачественной гиперплазией предстательной железы // Нефрология. – 2015. – Т. 19. – № 4. – С. 108–111. [Borovets SYu, Gorbachev AG, Al'-Shukri SKh, Rybalov MA. To pathogenetic substantiation of peptide bioregulators treatment courses in patients with benign prostatic hyperplasia. *Nephrology.* 2015;19(4):108-111. (In Russ.)]
60. Сорока И.В., Петленко С.В. Клинико-лабораторная эффективность монотерапии препаратом «Простатилен» (Prostatilenum) доброкачественной гиперплазии предстательной железы с синдромом нижних мочевыводящих путей // Медицинские новости. – 2012. – № 5. – С. 59–61. [Soroka IV, Petlenko SV. Clinical laboratory efficacy of Prostatilene (Prostatilenum) monotherapy of benign prostatic hyperplasia with lower urinary tract syndrome. *Meditsinskie novosti*. 2012;(5):59-61. (In Russ.)]
61. Аль-Шукри С.Х., Ткачук В.Н., Горбачев А.Г., и др. Уродинамические исследования в диагностике инфравезикальной обструкции у мужчин // Урология и нефрология. – 1998. – № 6. – С. 27–29. [Al'-Shukri SKh, Tkachuk VN, Gorbachev AG, et al. Urodinamicheskie issledovaniya v diagnostike infravezikal'noy obstruktsii u muzhchin. *Urol Nefrol (Mosk)*. 1998;(6):27-29. (In Russ.)]
62. Аль-Шукри С.Х., Амдий Р.Э., Кузьмин И.В. Снижение сократимости мочевого пузыря у больных доброкачественной гиперплазией предстательной железы // Урологические ведомости. – 2011. – Т. 1. – № 1. – С. 3–8. [Al'-Shukri SKh, Amdiy RE, Kuz'min IV. Decrease of urinary bladder contractility in patients with benign prostate hyperplasia. *Urologicheskie vedomosti.*2011;1(1):3-8. (In Russ.)]
63. Azadzoi KM, Tarcan T, Kozlowski R, et al. Overactivity and structural changes in the chronically ischemic bladder. *J Urol*. 1999;162(5):1768-1778.
64. Кузьмин И.В., Борискин А.Г., Слесаревская М.Н., Лукина Е.Е. Состояние микроциркуляции в стенке мочевого пузыря у больных с гиперактивностью мочевого пузыря // Нефрология. – 2008. – Т. 12. – № 2. – С. 70–74. [Kuz'min IV, Boriskin AG, Slesarevskaya MN, Lukina EE. The state of microcirculation in the urinary bladder wall in patients with hyperactivity of the urinary bladder. *Nephrology.* 2008;12(2):70-74. (In Russ.)]. https://doi.org/10.24884/1561-6274-2008-12-2-70-74.
65. Аль-Шукри С.Х., Кузьмин И.В., Борискин А.Г., и др. Коррекция нарушений микроциркуляции у больных с гиперактивностью мочевого пузыря // Нефрология. – 2011. – Т. 15. – № 1. – С. 58–64. [Al'-Shukri SKh, Kuz'min IV, Boriskin AG, et al. Correction of microcirculatory disorders in patients with overactive bladder. *Nephrology.* 2011;15(1):58-64. (InRuss.)]. https://doi.org/10.24884/1561-6274-2011-15-1-58-64.
66. Яицкий Н.А., Аль-Шукри С.Х., Горбачев А.Г., Айвазян И.А. Лечение острой рефлекторной задержки мочи после операций в области сфинктера прямой кишки // Вестник хирургии им. И.И. Грекова. – 1996. – Т. 155. – № 6. – С. 80–81. [Yaitskiy NA, Al'-Shukri SKh, Gorbachev AG, Ayvazyan IA. A correlation between the duration of post-injectional abscesses and biological features of the microorganisms responsible for them. *Vestn Khir Im II Grek*. 1996;155(6):80-81. (In Russ.)]
67. Амдий Р.Э., Аль-Шукри С.Х., Кузьмин И.В., и др. Опыт применения канефрона при лечении острого неосложненного цистита у женщин // Урологические ведомости. – 2016. – Т. 6. – № 2. – С. 16–22. [Amdiy RE, Al'-Shukri SKh, Kuz'min IV, et al. Use of Kanefron in treatment of acute uncomplicated cystitis in women. *Urologicheskie vedomosti.* 2016;6(2):16-22. (In Russ.)]. https://doi.org/10.17816/uroved6216-22.
68. Слесаревская М.Н., Кузьмин И.В., Жарких А.В., Шабудина Н.О. Оценка состояния микроциркуляции в стенке мочевого пузыря у женщин с хроническим рецидивирующим циститом // Урологические ведомости. – 2012. – Т. 2. – № 2. – С. 26–31. [Slesarevskaya MN, Kuz'min IV, Zharkikh AV, Shabudina NO. Assessment of microcirculation's condition of the bladder wall at women with chronic recurrent cystitis. *Urologicheskie vedomosti.* 2012;2(2):26-31. (In Russ.)]. https://doi.org/10.17816/uroved2226-31.
69. Михеев В.С., Болонина В.П., Горбачев А.Г. Модификация мутагенности лекарственных препаратов путем их иммобилизации: Эффект иммобилизации простатилена в поливиниловом

спирте у мышей // Генетика. – 1992. – Т. 28. – № 8. – С. 80–84. [Mikheev VS, Bolonina VP, Gorbachev AG. Modifikatsiya mutagennosti lekarstvennykh preparatov putem ikh immobilizatsii: Effekt immobilizatsii prostatilena v polivinilovom spirte u myshey. *Genetika*. 1992;28(8):80-84. (In Russ.)]

70. Шкундина И.С., Тер-Аванесян М.Д. Прионы // Успехи биологической химии. – 2006. – Т. 46. – С. 3–42. [Shkundina IS, Ter-Avanesyan MD. Priony. *Uspekhi biologicheskoy khimii*. 2006;(46):3-42. (In Russ.)]
71. Baviskar P, Bedse A, Sadique S, et al. Drug delivery on rectal absorption: suppositories. *Int J Pharm Sci Rev Res.* 2013;21(1):70-76.
72. Lakshmi PJ, Deepthi B, Rama Rao N. Rectal drug delivery: a promising route for enhancing drug absorption. *Asian J Res Pharm Sci*. 2012;2(4):143-149.
73. Jitendra, Sharma PK, Sumendha Bansal, Arunabha Banik Noninvasive routes of protein and peptides drug delivery. *Indian J Pharm Sci*. 2011; 73(4): 367-375. https://doi.org/10.4103/0250-474X.95608.
74. Метельский С.Т. Изучение пищеварения и всасывания в клинике // Поликлиника. –2014. – № 2. – С. 3–9. [Metel'skiy ST. Izuchenie pishchevareniya i vsasyvaniya v klinike. *Poliklinika*. 2014;(2):3-9. (In Russ.)]
75. Орлова О.В., Егорова С.Н., Ослопов В.Н. Исследование влияния диметилсульфоксида на проницаемость клеточных мембран // Казанский медицинский журнал. – 2011. – Т. 92. – № 6. – С. 901–904. [Orlova OV, Egorova SN, Oslopov VN. Investigation of the effect of dimethylsulfoxide on the permeability of cell membranes. *Kazan Med Zh*. 2011;92(6):901-904. (In Russ.)]

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