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Assessment of Efficiency and Safety of Phytocomposition with Prostate-Protective Properties in the form of Rectal Suppositories

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Abstract

AIM: To evaluate the clinical efficiency of phytocomposition with prostate-protective properties in the form of rectal suppositories.

METHODS: The analysis of literature information was performed to assess literature data and form an evidence base for the ratio between the levels of clinical effectiveness and safety for phytocomposition with prostate-protective properties in the form of rectal suppositories. To assess the clinical efficiency and safety the authors used a literature review on the ground of databases PubMed, MEDLINE, Web of Science, and Scopus.

RESULTS: The functional characteristics of a combination of extracts of saw palmetto, lovage roots, and calendula flowers are caused by fatty acids and their derivatives (saw palmetto), essential oils, flavonoids (lovage, calendula), phenolic acids, phthalides, and bitter principles (lovage). Considering the complex effect of all components, the studied phytocomposition in the form of rectal suppositories promotes the arrest of the inflammatory process, inhibits vein micro-thrombosis in the prostate, decreases the edema and leucocytic infiltration of the prostate, and improves microcirculation processes.

CONCLUSIONS: Analyzing the scientific literature on the components of phytocomposition of rectal suppositories with prostate-protective properties, it may be concluded that the combination of extracts of saw

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palmetto, lovage roots, and calendula flowers has anti-inflammatory, antiproliferative, and immunomodulatory action.

Keywords:

Chronic Prostatitis (CP), Benign Prostate Hyperplasia (BPH), phytopreparation, suppositories, efficiency, safety.

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Introduction

Prostatitis is an acute or chronic inflammation of the parenchymatous and interstitial tissue of the prostate (Sudeep et al., 2019). Chronic prostatitis (CP) is one of the most common diseases in males of reproductive age. According to available evidence, the majority of such patients (up to 60-65%) have a proper chronic abacterial prostatitis (CAP), which can later in younger patients cause disorders in their reproductive function (Chua et al., 2014; Vela-Navarrete et al., 2005). As is known, the basis for spermatogenesis disorders in CP are three interconnected factors: infectious-toxic factors, and immunological and hormonal factors (Sudeep et al., 2020). The consequences of chronic prostate inflammation include disorders in sex hormone metabolism, sperm transport, and sperm qualitative and quantitative parameters (Schinkovitz et al., 2008).

To resolve this medical-social issue a wide spectrum of pharmacotherapeutic agents is used. In chronic bacterial prostatitis, the antibacterial products form the first line of treatment (Klochko et al., 2023; Mansouri, 2023). At the same time, for various forms of CP, it is still necessary to use products with anti-inflammatory, antioxidative, and antiproliferative effects. In this case, herbal products have a large potential. One of the most common phytopreparations for CAP treatment is *Saw palmetto* – a dwarf palm. *Saw palmetto.* At present, berrie extract of saw palmetto is one of the most common herbal products, used mainly for symptomatic benign prostate hyperplasia (Sudeep et al., 2020).

Saw palmetto berries extract has anti-inflammatory, anti-exudative, anti-androgenic, and diuretic effects, stimulating neuroendocrine regulation of prostate function. The mechanisms of its anti-inflammatory and anti-exudative effects are based on the inhibition of prostaglandin synthesis, which causes a decrease in vessel wall permeability and edema of prostate tissues (Gorpynchenko et al., 2013; Galkin et al., 2019). The mechanism of its anti-androgenic effects is based on the inhibition of the activity of 5-alfa-reductase and aromatase – the key enzymes, playing an important role in pathogenesis of benign prostate hyperplasia. Under the effect of these enzymes, testosterone is biotransformed into dihydrotestosterone and estradiol, which causes the development of prostate hyperplasia (Gorpinchenko et al., 2023). The effect of saw palmetto berries extract in this case was more potent against symptoms of the lower urinary tract and uroflowmetry results than finasteride – 5-alfa-reductase inhibitor (Gorpynchenko et al., 2013; Zub, 2023).

During short-term clinical trials saw palmetto berries extract was useful for the improvement of prostate hypertrophy symptoms, however, it did not affect the prostate size or level of prostate-specific antigen (PSA) in blood serum.

Saw palmetto berries contain fatty acids and their derivative (caprinic acid, caprilic acid, laurinic acid, myristic acid, palmitic acid, stearic acid, and oleic acid), phytosterols (sitosterin, campesterin, stigmasterin), a small quantity of aliphatic alcohols, etc. *Saw palmetto* is available in several formulations, including liquid extracts, tablets, capsules, and suppositories (Sudeep et al., 2019).

The medical product in the form of rectal suppositories is a combination of herbal components, containing the following *active components:* saw palmetto berries extract (*Saw palmetto*) – 150 mg, lovage root extract (*Levisticum officinale*) – 50 mg, calendula flowers extract (*Calendula officinalis*) – 50 mg; excipients: solid fat (Mohandas et al., 2024; Madhavi et al., 2023).

This combination of phytocomponents promotes the arrest of inflammatory process, restoration of microcirculation, prevents microtrombosis development in prostate veins, decreases edema and leukocytic infiltration of prostate, improves processes of microcirculation and platelet-vessel hemostasis, stimulates muscle tone of urinary bladder, promotes elimination of disuric disorders, prevents destructive processes through inhibition of excessive free radicals oxidation, renders organotropic effect on prostate (prostate-protective effect), and has anti-inflammatory action (Chua et al., 2014; Galkin et al., 2019; Rauf et al., 2018; Cicero et al., 2019).

Suppositories are one of the most common forms; they are used for the treatment of urological, gynecological, and proctological diseases, etc. Rectal suppositories may have various types of action; they are prescribed both for the effects of their herbal substances, and resorptive effects.

The **principal aim** of this study was to evaluate the efficiency and safety of the rectal suppositories phytocomposition with prostate-protective properties.

Materials and Methods

To assess the clinical efficiency and safety the authors used a literature review, grounded on databases PubMed, MEDLINE, Web of Science, and Scopus, which included the following data: articles, found at the site through the Google search system, and links demonstrating safe and effective use of the rectal suppositories phytocomposition with prostate-protective properties in medicine.

The critical analysis of literature information was performed to assess the completeness of literature data and form an evidence base relating to the levels of clinical efficiency and safety for phytocomposition with prostate-protective properties.

During the preparation of the analysis, the authors collected data and principal information, necessary for the analysis (such as specifications, flow charts, bibliographic data, quality system documents, etc.), and also for study planning.

Pharmacognostic Characteristic of the Components of Phytocomposition

Saw palmetto – is a dwarf palm. The tree grows 6-10 feet high and has a crown consisting of big leaves. Native Americans have been using saw palmetto berries both as food and therapeutic agents for various diseases, including as a soothing, diuretic, hypnotic agent, expectorant and antitussive agent, and a remedy for lactation, infertility, digestive disorders, and problems with urination (Sudeep et al., 2019).

Extract of saw palmetto berries (*Saw palmetto*) contains a large number of useful elements and compounds (P, Mg, Fe, Zn), volatile oils, free fatty acids, and sterines, inhibiting 5-alfa-reductase and converting testosterone into dihydrotestosterone, which was demonstrated *in vitro*. About 63% of the content is comprised of free fatty acids, including caprinic acid, caprilic acid, caproic acid, laurinic acid, palmitic acid, and oleic acid. The other part contains ethyl ethers of these fatty acids and sterines, including beta-sitosterin and its glucoside. It is perceived that fat-soluble compounds are the principal pharmacological components.

Other components of saw palmetto berries include proanthocyanidins, carotenes, lipase, tanning agents, and sugars (Chua et al., 2014; Dubova et al., 2022).

The purified fat-soluble extract, which is the most studied from therapeutic point, contains 85% – 95% of fatty acids and sterols. It contains mostly a complex mixture of saturated and unsaturated free fatty acids, their methyl and ethyl derivatives (about 7%), long-chain alcohols in free and etherized forms, as well as various free and etherized sterol derivatives.

Extract of *Saw palmetto* berries actively stimulates healthy functioning of hormonal system and promotes normalization of sex hormone ratio in the body; it promotes testosterone production and improves sperm quality, helps slow down or completely prevent inflammatory diseases or prostate adenoma in males of various ages, as well as decreases the urinary urge frequency and significantly improves the process of urination, increases libido, improves reproductive capacities, and sustains natural tone (Vela-Navarrete et al., 2005; Llopiz-Guerra et al., 2024).

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Lovage (*Levisticum officinale*) is a well-known aromatic herb, widely used in food products as an aromatizer, and in cosmetic and medical products. Lovage is an erect perennial herb, 1.8-2.5 m high with the socket of radical leaves and stems with further leaves; its flowers form umbel inflorescence at the apex of stems. The stems and leaves are shiny and naked, from green to yellow-green colour. The larger radical leaves are up to 70 cm long, tripartite, with wide triangle or diamond-shaped acutely pointed leaves with several marginal teeth; the stem leaves are smaller and less separated, with several leaflets. The flowers are of yellow to greenish-yellow colour, 2-3 mm in diameter, forming round umbels up to 10-15 cm in diameter.

The principal components of lovage extract are terpenes and phthalides, β-phellandrene, α-terpinyl acetate, and Z-ligustilide; the principal components are presented in various proportions in different plant organs. Although lovage biological activity was not subject to extensive studies, it was shown that lovage extract components have antimicrobial, anti-oxidative, and other effects. It was reported that Z-ligustilide demonstrates various effects on health, such as anti-inflammatory, anti-tumour, and anti-thrombotic activity, as well as a positive effect against neurological disorders (Schinkovitz et al., 2008).

Lovage root *(Levisticum officinale)* contains essential oil, which principal component (about 70%) is a series of lactone derivatives - phthalides (alkyl phthalides: 3-n-butyliden phthalide (ligasticum lactone), 3-n-butyliden-4,5 dihydrophthalide (ligustilide), ternine, senkiunolide, angeolide, levistolide). Other biologically active components are terpenes (α-pinene, β-pinene, pentyl cyclohexadiene, phellandrene, α-terpineol), phenolic acids (caffeic, benzoic, chlorogenic, ferulenic acid), coumarins (coumarin, umbelliferone), polyenes (falcarindiol), ethers of acetic and valerianic acids and free acetic, isovalerianic, butyric and benzoic acids, lecithin, malic and angelic acids, tanning substances, macro-, and microelements:

Ca, Fe, Cu, Mn, Zn, Co, Ni, Cr, Ba, Se, Sr, Ti, Rb, Mo, Pb, Zr, Cd, V, As, Sn, Ag, Bi, Cs, Hg, Sb, Sc; and also starch, gum, and resins. Falcarindiol from lovage root was identified, as an antibiotic.

Lovage root extract (*Levisticum officinale*) – contains essential oils, phthalides (ligustilide, butyl phthalide), furocoumarins (psoralen, bergapten), phenolcarbonic acids, resins with spasmolytic, antimicrobial, anti-inflammatory, disinfectant, diuretic and mucolytic effects, and also it improves digestion and appetite, prevents meteorism, and efficiently eliminates excess salts (Miran et al., 2018).

Calendula (*Calendula officinalis*) is a plant species of the chamomile family. *C. officinalis* is a short-living aromatic perennial plant, reaching 80 cm (31 inches) in weight, with sparsely branched limp or erect stems. Its leaves are oblong-lanceolate, 5-17 cm (2-7 inches) long, hairy on both sides with even margins, or with rarely wavy or slightly toothed margins. Inflorescences are yellow, consisting of a thick flower head 4-7 cm in diameter, surrounded by two rows of hairy bracts; wildflowers have one ring of ray flowers, surrounding the central disc flowers. The disc-shaped inflorescences are tubular and hermaphrodite, generally of a more intense orange-yellow colour than the female flowers; they are tridentate, peripheral ray inflorescences.

Calendula flowers contain triterpene glycosides and aglycones, carotinoids, and essential oils. Calendula has a nourishing effect on the skin and is used topically for wound healing due to its calming and antimicrobial properties. It is also useful in gingivitis, radiation mucositis, vaginal candidosis, healing of episiotomy, chronic prostatitis, diaper dermatitis, leg lesions (venous and neuropathic), and in radiation dermatitis. The extract has anti-inflammatory, cytotoxic, and anti-tumour effects (Final Report, 2001).

Calendula flower extract is obtained from flowers of *Calendula officinalis*. The extract contains sugars, carotinoids, phenolic acids, sterines, saponines, flavonoids, resins, sterines, quinones, mucus, vitamins, polyprenyl quinones, and essential oils. The results of HPLC analysis (High Performance Liquid Chromatography) demonstrate that calendula flower extract contains nine different active compounds, including vitexin 11.40%, rutin 12.29%, quercetine-3-3 galactozide 12.64%, luteolin-7-glucose 9.27%, quercetine-3-glucoside 7.38%, quercitrin 9.83%, myricetin 10%, luteolin 10.72%, apigenin 7.08%, and kaempherol 9.37%. Extract of calendula is used both as an individual product and in the content of various compositions, such as medicinal products, medical devices, and cosmetic products. The studies of acute toxicity in rats and mice show that the extract is relatively non-toxic. Animal tests demonstrated at maximum some skin irritation and absence of sensitization or phototoxicity (Morgia et al., 2017).

Review of Clinical Efficiency of Phytocomposition in the Form of Rectal Suppositories

The above phytocomposition is used as a hygienic and preventive agent in the following diseases and conditions: chronic prostatitis of various genesis; prevention of chronic prostatitis exacerbation in the presence of risk factors (smoking, alcohol abuse, stress, hypodynamia, irregular and messy sexual life, sexually transmitted diseases and history of chronic diseases of other organs, age over 40 years); benign prostate hyperplasia, complications after prostate surgery, and age-related dysfunction of prostate (Nikitaev, 2023).

The efficiency and safety of the suppositories were assessed based on individual preclinical studies and the results of specific clinical trials. All ingredients in the phytocomposition have proven themselves well.

Saw palmetto is a unique phytotherapeutic agent with efficiency checked in multiple studies, using saw palmetto-based products in patients with benign prostate hyperplasia (BPH) and chronic prostatitis.

The largest meta-analysis of Serenoa repens (*Saw palmetto*), published today shows that the use of this agent significantly improves urination symptoms and increases urination rate, on average, by 1.93 ml/sec. Compared to placebo (Tacklind et al., 2012).

It has been established that *Saw palmetto* extract and finasteride decrease symptoms of prostate adenoma by IPSS (International Prostate Symptom Score), improve life quality, and increase peak urination velocity in equivalent mode, however, the patients, who use *Serenoa repens* (S) experienced an improvement in libido and sexual vigor. The studies have demonstrated that Serenoa repens (*Saw palmetto*) and tamsulosine (alfa-adrenoblocker) equally improve IPSS and peak urination velocity in 12-month therapy of lower urinary tract symptoms in BPH patients. Both components were tolerated well, however, in the tamsulosine group ejaculation disorders were relatively frequent (Kwon, 2019).

Because phytotherapy is associated with minimal adverse effects, its role in the prevention of BPH progression has been thoroughly studied. In the latest prospective study, involving males with moderate symptoms of urinary bladder obstruction (IPSS<8) *Saw palmetto* extract demonstrated promising results during a 24-month period. Compared to the control group, the level of progression (namely, progression of symptoms and/or cases of acute urinary retention), was significantly lower at the end of the study (16% versus 22%, p=0.03). The reliable improvements in IPSS, life quality, and peak urination velocity were also demonstrated in *Saw palmetto* group.

Several modern studies demonstrated the anti-proliferative and pro-apoptotic action of saw palmetto extracts, closely associated with anti-inflammatory response of BPH cells. As appears, interleukin-moderated growth of BHP cells is modified under the effect of *Saw palmetto* extract (Debruyne et al., 2002; Trivisonno et al., 2021).

Inflammatory processes may disorder delicate balance between cell growth and death, enhancing proliferation and reducing apoptosis. However, in *in vitro* experiments, researchers established cross-alignment of all these processes under the effect of the studied extract. Also, microarray analysis demonstrated the upregulation of multiple metalloproteins in BPH cells under the effect of *Saw palmetto*. This may be an important discovery, as it is believed that metalloproteines are associated with the regulation of many cellular processes, including gene expression, apoptosis, proliferation, differentiation, and inflammation (Carraro et al., 1996).

The known anti-androgenic mechanism of saw palmetto berries extract effect is due to the inhibition of 5α-reductase with a further decrease in the production of dihydrotestosterone, causing a decrease in the proliferation of acinus cells of the prostate.

American researchers have proved that saw palmetto berries extract has a stable therapeutic effect in cessation of symptoms of the lower urinary tract in CP in case of prolonged continuous use (Boyle et al., 2000).

The results of meta-analysis of 12 studies showed that on the background of the use of saw palmetto berries extract the level of nocturia decreased by 25% versus placebo (Vela Navarrete et al., 2005).

Colado-Velázquez et al., noted that saw palmetto berries extract (another name – Sabal palm) has an anti-oxidative effect due to the inhibition of expression of genes of pro-inflammatory cytokines, tumour necrosis factor (TNF-α), interleukines (IL-1β and IL-6), and growth factors of fibroblasts (FGF) and endothelium. Also, the authors detected that the extract's anti-oxidative properties were enhanced due to its anti-inflammatory effect, as it was able to inhibit the production of metabolites of 5-lipoxygenase and leukotrienes (Colado-Velázquez et al., 2015).

The current studies demonstrate that saw palmetto berries extract (Sabal palm) contains a unique complex of fatty acids, capable of maintaining and stimulating the male reproductive system (Table 1).

Table 1. Content of phytosterines and fatty acids in saw palmetto berries extract (Penugonda & Lindshield, 2013; Sirab et al., 2013; Stamatiou & Pierris, 2013).

Name	Type	Mechanism of action
Capric acid	Saturated fatty acid	Anti-oxidative and anti-inflammatory activity; decreases the production of active forms of oxygen and nitric oxide radicals, transcriptional activity of nuclear factor (NF-κB) and cyclo-oxygenase activity (COX-2), and prevents expression of chemotaxis genes in monocytes
Lauric acid	Saturated fatty acid	Anti-oxidative and anti-inflammatory effects, capacity to inhibit COX-2 enzyme
Caprylic acid	Saturated fatty acid	Anti-oxidative effect and inhibition of chemokine IL-8 production
Linoleic acid	Saturated fatty acid	Anti-oxidative activity: decreases expression of genes of factor NF-κB and production of iNOS, free radicals; anti-inflammatory activity – decreases COX-2 enzyme
Myristic acid	Saturated fatty acid	Potent absorber of nitric oxide, superoxide, hydroxide, and lipid peroxides
Palmitinic acid	Saturated fatty acid	Inhibits production of pro-inflammatory cytokine TNF-α
Oleic acid	Unsaturated fatty acid	Potent anti-oxidant, capable of inhibiting activation of transcriptional factor NF-κB and production of free radicals and active forms of oxygen; also, has anti-inflammatory effect, due to decrease of expression of COX-2 and prostaglandins E-2
β-sitosterin	Phytosterin	Antioxidant: increases activity of enzymes superoxide dismutase and glutathione peroxidase

In the clinical study, examining the role of phytotherapeutic agents in the treatment of patients with chronic renal diseases (n=56), an extract of *Saw Palmetto* was used for 8 weeks after the main course of antibacterial therapy. In the result, the authors detected in the main study group a reliable decrease in pain syndrome and an improvement in urination quality (De Monte et al., 2014).

Saw palmetto extracts render a spasmolytic effect on smooth muscle. First, it was shown that *Saw Palmetto* extract inhibited rat smooth muscle through inhibition of calcium ion influx. The later studies demonstrated that *Saw Palmetto* extract permanently inhibited α1-adrenergic properties of human receptors in studies *in vitro*. If this effect is clinically significant, it remains still unknown (Sirab et al., 2013).

Another study proves the effect of saw palmetto berries extract on a decrease of cell proliferation in the prostate, which allows using this phytocomponent both for the prevention of benign prostate hyperplasia (BPH) in young males with prostatitis, and for the treatment of lower urinary tract symptoms in BPH and CP in middle-aged and elderly males (Yang & Te, 2005).

In a double-blind comparative study, 542 males with BPH symptoms were randomized for α-blocker tamsulosine or *Saw Palmetto* extract for 1 year. Both groups demonstrated identical levels of symptom improvement. In the patient subgroup of the most severe BPH in this study, *Palmetto* extract statistically exceeded tamsulosine for symptom relief. The addition of Serenoa extract to tamsulosine did not change

adverse effects. A 6-month double-blind study of *Saw Palmetto* extract in 60 males revealed results, very close to the above two studies, although it also demonstrated equivalent improvement of flow velocity between the groups (Gordon & Shaughnessy, 2003).

In the opinion of De Monte C. et al., palmetto berries extract induces apoptosis, inhibits the secretion of IL-12, monocytic chemotactic protein (MCP-1), and, as a result, causes a decrease of inflammatory reaction in chronic prostatitis. The authors are convinced that among phytotherapeutic products, used for prostate diseases, the bioactive compounds extracted from saw palmetto berries are the most common due to their safety, tolerability profile, and clinical benefits. Sabal palm extract has a low cytotoxicity against normal cells and promotes a decrease in cell growth in a dose-dependent manner (De Monte et al., 2014).

Several clinical studies show that *Saw Palmetto* extract may have clinical benefits in chronic prostatitis or pelvic pain. One double-blind randomized study compared monotherapy with *Saw Palmetto* extract compared to the treatment with extract of *Saw Palmetto*, selene, and licopene in males with non-bacterial chronic pelvic pain. After 8 weeks both groups demonstrated equivalent symptom improvement, while only the combined product decreased levels of PSA and leukocytes in urine (Djavan et al., 2005; Vela Navarrete et al., 2005).

One study used a combination of *Saw Palmetto* extract 160 mg, root extract of *Urtica dioica* 120 mg, quercetine 100 mg, and curcumin 200 mg once daily with antibiotic prufloxacin 600 mg once daily in males with bacterial prostatitis. One-fourth of 143 study subjects were randomized to receive monotherapy with prufloxacin. The treatment duration was 14 days. One month after the treatment the patients from combined group had significantly more chances (88% versus 27%) to be asymptomatic compared to the group with only antibiotics. Further randomized studies confirm that the use of *Saw palmetto* extract, both as monotherapy and as a combination with selene, lycopene, bromelain, and methyl sulfonyl methane or arbutin and *Lactobacillus sporogenes* increases antibiotic efficiency in patients with chronic prostatitis (Yarnell, 2002).

The studies of the clinical effect of lovage essential oil revealed its antimicrobial and antifungal effects, as well as diuretic effect and the ability to eliminate meteorism. The principal component of its essential oil – ligastilide – causes spasmolytic effect. Certain phthalides (such as sedanolide, and senkiunolide) have antioxidative effects and inhibit cyclooxygenase (Schinkovitz et al., 2008).

The scientists revealed the anti-tumour activity of lovage roots (*Levisticum officinale*). This herb has been used for centuries in folk medicine due to its antiflatulent, spasmolytic, and diuretic properties (Yarnell, 2002).

The antibacterial activity of *L. officinale* is associated with polyacetylenes contained in the extract, such as 3(*R*)-falcarinol and 3(*R*)-8(*S*)-falcarindiol. Polyacetylenes of falcarinol type demonstrate many interesting biologically active properties, including anti-inflammatory, antibacterial, anti-aggregative, cytotoxic, and anti-tumour properties. There is data that the cytotoxic effect is caused not by falcarinoles, but by another component – terpinyl (Schinkovitz et al., 2008).

Lovage extract (*L. officinale*) demonstrates considerable antibacterial and antifungal properties in the concentration range of 0.015-0.030%. It may be noted that the antimicrobial properties of lovage extract are caused by a high content of β-phellandrene (RT = 6.536, 22.39%), α-terpinyl acetate (RT=14.859, 30.99%), and (Z)–ligustilide (RT = 23.942, 11.19 %). The above-mentioned compounds possess active antimicrobial properties due to the following mechanisms: the destruction of the cell wall and cell membrane, decrease of

peri-nuclear cytoplasm, damage of lipid fraction in the cell membrane, causing changes in the membrane permeability and outflow of intracellular content.

In vitro tests have shown that the minimal bactericidal and fungicidal concentrations of oil, extracted from *Levisticum officinale* against *Bacillus subtilis, Pseudomonas fluorescens, Xanthomonas campestris, Erwinia amylovora, Erwinia carotovora*, and *Candida utilis*, are relatively low (0.015-0.03 %), which suggests high antibacterial and antifungal activity of the product (Metzger et al., 2008).

It is known that chlorogenic, caffeic, and ferulic acids, extracted from *Levisticum officinale* have antioxidative properties, while rosmarinic acid has a potent antioxidant effect. Animal studies have demonstrated that chlorogenic acid increases insulin sensitivity and improves glucose tolerance and lipid metabolism. Ferulic acid has antihypertensive effect and decreases the risk of diabetes type II, obesity, Alzheimer's disease, eclampsia, and stroke. Rosmarinic acid has anti-apoptotic and anti-inflammatory effects and may play an important role in anti-nociceptive properties (Ciocarlan et al., 2018).

Luteolin, as a representative of the flavonoid class, apart from its anti-oxidative effect has anti-inflammatory properties. Menthofuran from stems of *Levisticum officinale* is closely associated with an anti-oxidative effect, caused by its ability to entrap radicals. Studies have shown that alcohol-water extract from stems of *Levisticum officinale* contains flavonoids – luteolin, quercetine, rosemarine, caffeic, and hexanoic acids, which have the maximal inhibiting capacity towards α-amylase and may cause anti-dyslipidemic effect (Ciocarlan et al., 2018).

Alcohol-water extract from roots of *Levisticum officinale* can cause the death of leukemic cells and inhibit the growth in the lines PC3 and DU145 of tumour cells of the prostate. It is presumed that such an effect is associated with the presence of polyacetylenes – falcarinol and falcarindiol. There is data that the extracts with high concentrations of falcarinol have, as a rule, the maximal inhibiting effect on cancer cell growth compared to falcarindiol, another representative of this group.

Cytotoxicity of essential oil from *Levisticum officinale* leaves was estimated against squamose-cell cancer of the head and neck, with a principal fraction containing monoterpenes, with the most common α-terpinyl acetate (48.15%). At that, the researchers did not detect falcarinol in the essential oil. The authors did not find in the literature any data, confirming anti-tumour activity of α-terpinyl acetate, however, they presumed that namely, this component of essential oil possessed cytotoxic effects against tumour cells UMSCC1 (Gijbels et al., 1982).

The researchers studied the effect of alcohol-water extract of *Levisticum officinale* on steroid hormone synthesis *in vitro*. As a result, they detected concentration-dependent changes in steroid genesis, membrane integrity, cell viability, and intercellular communication in Leydig cells. Lower doses positively influenced cellular parameters, while larger doses (150-300 μg/ml) stimulated toxic effects, mediated by the decrease in membrane viability and inhibition of intercellular communications through gap junction in Leydig cells. These effects are associated with the influence of phenols and phenolic compounds in *Levisticum officinale* extract, with such dominating compounds, as cinaroside, kaempherol, rutin, chlorogenic and neochlorogenic acids. Similar results were obtained when studying the effects of biologically active substances in *Levisticum officinale* extract on spermatozoa mobility, while experimental data confirm the potential anti-oxidative effect of lower extract doses, and, therefore, a positive effect on reproductive function (Metzger et al., 2008).

Due to the complex bioactive substances and individual components, isolated from various parts of *Levisticum officinale* plant with a wide spectrum of pharmacological action, this herb has a promising use in medical and pharmaceutical practices.

The medicinal properties of calendula flowers are based on a wide spectrum of biologically active substances, namely: carotenoids, flavonoids, triterpene saponins, and the entire series of accompanying substances. The flowers, harvested at flowering stage, contain carotenoids, as a major group of biologically active substances – up to 3% (β-, γ-, δ-carotin, lycopene, xantophile, lutheine), zeaxanthin, violaxanthin, flavochrome, citraxanthine, neolycopene, chrysanth, rubixanthin, neurosporin, phytoene, phytofluin (Santos et al., 2005).

Another group of biologically active substances is presented by flavonoids (up to 4%), in particular, glycosides of kaempherol, quercetine, and isorhamnetin. The group of biologically active compounds in calendula flowers includes saponins (calendulosides – glicosides of oleanolic acid). Calendula flowers also contain phytoncydes, bitter principles (calenden), tanning substances, essential oils, resins, albumin, mucus, nitric compounds, organic acids: maleic, pentadecylic acids, and traces of salicylic and ascorbic acids; and traces of alcaloids. Calendula contains the following macroelements: Ca, Mg, Fe; microelements: Mn, Cu, Zn, C, Mo, Cr, Al, Se, Ni, Sr, Pb, I, B. The most concentrated in calendula are Zn, Ci, Mo, and Se (Sirab et al., 2013).

The active pharmacological study of this plant extract, as an anti-inflammatory agent led to its use in some phytopreparations for urinary tract infections in urology.

Phytopharmaceutical studies of various forms of calendula extract showed its anti-inflammatory, antiviral, and anti-genotoxic properties, which were of therapeutic interest (Kalvatchev et al., 1997; Pérez-Carreón et al., 2002; Yoshikawa et al., 2001).

The recent studies also clearly demonstrated the anti-tumour and immunomodulating activity *in vitro* and anti-tumour effect *in vivo*. This extract potently inhibits many tumour cell lines, at the same time promoting the proliferation and activation of peripheral lymphocytes. The mechanism of this inhibition consists of cell cycle arrest at G0/G1 and apoptosis induction. Cell cycle arrest at G1 is caused mainly by the weakening of the expression of cyclines D1, D3, E, A, and CDK1 Cdc2, CDK2, CDK4, and CDK6. Besides, *Calendula officinalis* extract causes induction of apoptosis through activation of caspase-3-dependent mechanisms only in tumour cells, which is of advantage, as these products can be used in live organisms (Jiménez-Medina et al., 2006).

As to enhancement of peripheral lymphocyte proliferation, it was observed in CD4+, CD19+, and mostly in CD3+/CD16/56+. Such activation causes mostly the stimulation of lymphocyte anti-tumour activity, which may confirm anti-cancerogenic effect of calendula extract *in vivo*.

Another study also established various activities of *Calendula officinalis* extract, in particular, antibacterial, antifungal, antiviral, anti-inflammatory, anti-tumour, and wound-healing properties of calendula (Efstratiou et al., 2012; Preethi et al., 2009; Lovecka et al., 2017).

Methanolic and ethanolic extracts of *Calendula officinalis* flowers were separately tested on the group of pathogenic microorganisms, including *Bacillus subtilis* NCTC 10400 [JEM7], *Pseudomonas aeruginosa* NCTC 27853 [JEM16], *Bacillus cereus* 444C (collection *Bacillus cereus* 44444C), ampicillin-resistant *E. coli* (collection UUC), *E. coli* NCTC 12900 [JEM4], *E. coli* NCTC 25922 [JEEM17], *Staphylococcus aureus*

MSSA 25923 [JEM18], *Klebsiella aerogenes* [NCTC 952], *Klebsiella aerogenes* [NCTC 952] 775 [JEM10], *Bacillus pumilis* [JEM15], *Klebsiella pneumoniae* 700603 [JEM19]; and pathogenic fungi, including *Candida albicans* 0103 (collection UUC), *C.albicans* ATCC 90028, *Candida krusei* ATCC 6258, *Candida glabrata* ATCC 2001, *Candida parapsilosis* ATCC 22019, *Aspergillus flavus* GC 6158, *Aspergillus fumigatus* 27.5, *Aspergillus niger* 27.5 and *Exophiala dermatitidis* GC 7895 (Della Loggia et al., 1994).

Methanolic and ethanolic extracts of *Calendula officinalis* flowers exhibit various antimicrobial activities, shown by growth inhibition zones. The results of the disc diffusion assay have shown that the tested extracts of *Calendula officinalis* petals have a comparative antibacterial effect against gram-positive and gram-negative bacteria. In addition, methanolic extract demonstrated more inhibition of the majority of bacteria, than ethanolic extract. However, ethanolic extract demonstrated better antimicrobial activity against *S. aureus* MSSA 25923 and *E. faecalis* NCTC 775 (respectively, 28 and 18 mm), compared to methanolic extract (respectively, 18 and 14 mm) (Klouchek-Popova et al., 1984; Elias et al., 1990).

The results of the disc diffusion assay of fungi strains showed excellent antifungal activity. The results were comparable with standard product fluconazole (Morgia et al., 2017).

A potent anti-inflammatory reaction of *Calendula officinalis* extract may be mediated by the inhibition of anti-inflammatory cytokines and COX-2 and further synthesis of prostaglandines (Jambor et al., 2021).

Therefore, based on new literature data, the medicinal products based on *Calendula officinalis* extract have a wide spectrum of biological activity, including anti-inflammatory, spasmolytic, choleretic, antimicrobial, soothing, anti-edemic, antitoxic, hyposensitizing, anti-mitotic, reparative, antiviral, and wound-healing properties. Calendula improves metabolism and increases prostate secretory activity.

After analyzing the scientific literature on the components of this phytocomposition it may be concluded that the combination of extracts of saw palmetto, lovage roots, and calendula flowers has a anti-inflammatory, antiproliferative, and immunomodulating properties.

The functional properties of this combination of extracts of saw palmetto, lovage roots, and calendula flowers are caused by fatty acids and their derivatives (saw palmetto), essential oils, flavonoids (lovage, calendula), phenolic acids, phthalides, and bitter principles (lovage).

The mechanism of anti-inflammatory and anti-exudative effects of the combination of extracts of saw palmetto, lovage roots, and calendula flowers is based on the inhibition of prostaglandin synthesis by fatty acid fraction of saw palmetto berries extract, which causes the decrease in vessel wall permeability and resolution of prostate tissue edema. Besides, the anti-inflammatory properties are caused by calendula flower flavonoids due to the improvement of epithelization and the increase in local protective mechanisms (Gorpynchenko et al., 2013).

Antimicrobial (including antifungal and antiviral) effects of the product are caused by essential oils of lovage and calendula. Essential oils destroy the cell membranes of bacteria and decrease their aerobic respiration activity, which causes less energy production necessary for the synthesis of various organic substances. Essential oils also expand vessels, which increases the blood supply. Flavonoids from calendula are capable of binding to cell wall proteins and destroying bacterial cellular membranes.

The advantage of using a combination of extracts from saw palmetto, lovage root, and calendula flowers is also its combination of antimicrobial and anti-inflammatory effects, especially valuable in chronic processes in the male reproductive system. In addition, the production urine of sulfated organic acids and their

glucuronidized metabolites, which are sulfated, causes changes in urine acidity that prevent bacterial growth (Gurzhenko et al., 2018; Goroviy et al., 2014; Gorpynchenko & Sytenko, 2016; Gorpynchenko et al., 2021; Stamatovska & Nakov, 2022; Belenichev et al., 2023).

Spasmolytic (anticholinergic) effect is caused by flavonoid compounds. It is also provided by lovage phthalides: butyliden phthalide and ligastilide. Some phthalides from lovage root extract (for example, sedanolide, senkuinolide) render antioxidative effect and promote the organ defense from damage with free radicals.

Anti-androgenic effect of the studied suppositories is caused by the capacity of the compounds of saw palmetto extract to inhibit the activity of the key enzymes, that play an important role in pathogenesis of prostate benign hyperplasia (Gorpynchenko et al., 2015; Krasovskyi et al., 2022).

Anti-toxic, hyposensitizing, antimitotic, antimutagenic, and reparatory action of calendula flower extract causes organotropic effects on prostate, at the same time rendering prostate-protective effects and stimulating urinary bladder muscle tone (Dmytrenko et al., 2021).

Thus, the phytocomposition to be considered helps to reduce the inflammatory process, restore microcirculation, and prevent the development of microthrombosis of the veins of the prostate gland. Contributes to the reduction of edema and leukocyte infiltration of the prostate gland, improvement of the process of microcirculation, and platelet-vascular hemostasis. Stimulates the muscle tone of the bladder, and helps to eliminate dysuric disorders. Prevents destructive processes due to inhibition of excess oxidation of free radicals. It has an organotropic effect on the prostate gland (prostatoprotective effect). The most studied effect is the inhibitory activity of the phytocomposition against 5α-reductase, due to the non-selective inhibition of 5α-reductase isoenzymes type I and type II, as well as a decrease in the level of dihydrotestosterone, inhibition of testosterone-induced hypertrophy and antitumor effect.

However, the phytocomposition has certain limitations in its application. The moderate choleretic effect, due to the biologically active substances of lovage, imposes restrictions on the use of the phytocomposition for gastric and duodenal ulcers in the acute stage. The components of the phytoextract affect the composition of urine, primarily the excretion of urea, so its use in acute glomerulonephritis and pyelonephritis is not justified. Since the action of the extract from the fruits of *Serenoa repens* is associated with its antiandrogenic effect, namely with the blocking of the binding of dihydrotestosterone to the receptor that inhibits the activity of 5-a-reductase, it is undesirable to use the investigated phytocomposition in benign prostatic hyperplasia in the decompensation phase (Kwon, 2019). In isolated cases, the interaction of saw palmetto extract with warfarin has been reported (Izzo & Ernst, 2009). In general, taking into account the polyphytochemical composition of the product, individual hypersensitivity and the development of allergic reactions may be observed when using it.

Conclusions

The content of the examined phytocomposition has unique properties. Saw palmetto berries extract has a proved by the results of many randomized studies' effect on lower urinary tract syndrome, in particular, it improves IPSS score, life quality, and urination velocity. Besides, it mediates anti-inflammatory effect due to the inhibition of proinflammatory cytokines, which moderates the anti-proliferative effect and may prevent BPH progression.

High doses of lovage extract have an anti-tumour effect, and in small concentrations (like in the studied suppositories) the extract also possesses anti-inflammatory properties.

Calendula extract also renders anti-inflammatory effects, and moderate immunomodulatory, antibacterial, and regeneratory effects (due to stimulation of proliferation and migration of fibroblasts).

The combination of these agents may potentiate each other action, in particular, stimulate pro-inflammatory cytokines and increase apoptosis. Certainly, such a combination becomes irreplaceable in any inflammatory diseases of the lower urinary tract, especially in CP, whose pathogenesis is based on the disbalance of pro- and anti-inflammatory cytokines and disorders of apoptosis. The unique influence of this combination is its anti-proliferative effect, both direct and indirect, through affecting inflammation.

Considering the complex action of all its components, the studied phytocomposition in the form of rectal suppositories promotes the arrest of inflammatory process, prevents the development of microthrombosis in prostate veins, decreases edema and leukocytic infiltration in the prostate, and improves the processes of microcirculation and platelet-vessel hemostasis.

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Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

All authors' contributions are equal for the preparation of research in the manuscript.

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