Pygeum africanum Lipidic Extract

For the Treatment of BPH
EUROMED HERBAL EXTRACTS SERIES 5. PYGEUM AFRICANUM

Introduction

EUROMED is a company that specializes in making botanical extracts and active principles used as phytomedicines in pharmacy. EUROMED develops and produces therapeutically active raw materials.

The botanical raw materials are subject to strict selection and inspection, and products are manufactured according to methods developed by the EUROMED company. They include inspections to guarantee a standard quality from both analyticochemical and therapeutical points of view and take into consideration the state of art in different fields: research and development, analyses, processes and devices and therapeutic applications.

EUROMED guarantees the quality of its products by a broad phytochemical know-how.
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1 Pygeum africanum Lipidic Extract:
General Information

1.1 Description

The lipidic extract of Pygeum africanum is a standardized herbal extract of *Prunus africana* bark.

*Herbal remedy to prevent or treat BPH*

The trunk bark extract of Pygeum africanum is used as a herbal therapeutic agent in the treatment of benign prostatic hyperplasia (BHP) stage I - II which gives relief of the following symptoms:
- diurnal and nocturnal pollakisuria (frequent urination)
- micturition disorders

Residual urine is reduced and urinary outflow improved.

The Pygeum africanum extract from EUROMED gives most patients some relief of symptoms within the first 30 to 60 days.

The extract of Pygeum africanum does not interact with other drugs.
1.2 Indications

The lipidic extract of Pygeum africanum manufactured by EUROMED is used in the treatment of prostatic diseases, especially benign prostatic hypertrophy (international stages I-II, stages II-III according to VAHLEN SICK), and for the stabilization of the patient's urodynamics.

1.3 Extract Specifications

Pygeum africanum extract is a lipidic extract of Prunus africana containing minimum 13% of sterols as β-sitosterol. Finished preparations usually contain about 25-30 mg Pygeum africanum extract (as available from EUROMED) corresponding to 5-6 g of the bark.

1.4 Dosage and Methods of Administration

A daily oral dose of 75-200 mg of Pygeum africanum extract is common practice. Table 1 gives a survey of popular Pygeum africanum preparations available on the market.

1.5 Contraindications and Interactions

There are no known contraindications to the long-term use of Pygeum africanum extract. There are no known interactions with drugs usually prescribed.
1.6 Side-effects

Pygeum africanum extract is generally well tolerated. Side effects are rare when the standardized extract is taken. In exceptional cases gastric complaints may occur.

Tab. 1: Preparations containing Pygeum africanum extract.

<table>
<thead>
<tr>
<th>Preparation Name</th>
<th>Content of Pygeum Extract [mg]</th>
<th>Total extract/day [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tadenan</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Pronitol</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Prostamol</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Tebetane</td>
<td>30</td>
<td>120</td>
</tr>
<tr>
<td>Neourgenin</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Prostatonin</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Catiz</td>
<td>30</td>
<td>90-120</td>
</tr>
<tr>
<td>Ultracal</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Prostem</td>
<td>30</td>
<td>120</td>
</tr>
<tr>
<td>Rotamat</td>
<td>30</td>
<td>90-120</td>
</tr>
<tr>
<td>Tacril</td>
<td>30</td>
<td>90-120</td>
</tr>
</tbody>
</table>

2 From Plant to Extract
2.1 Pygeum bark (Pruni cortex):

Botanical Data

The genus *Prunus* has about 100 species, mainly in the Northern Hemisphere. Among them there are many ornamental or useful trees like cherry, plum and peach. One species, belonging to the previously separate genus *Pygeum*, occurs in the southern part of Africa.

*Prunus africana* (Hook.f.) Kalkm. [syn. *Pygeum africanum* Hook.f.] is an evergreen tree up to 25 m height, with a stem diameter about 1 m. The bark is dark and rugged, the branches brown and corky, and the twigs knobbly.

The heavy shining foliage is composed of simple leaves, arranged alternately, oval or lance-shaped, sometimes widely so, tapering at both ends and sometimes with a long drawn-out point or with a rounded apex and base. They are 3.8–10 cm long, shiny deep green above, duller and lighter below, with conspicuous veins and a distinct midrib which is prominent below. The margins may be toothed or untoothed. The leaf stalks are often pink or red.

Flowers, small, white, greenish, hairy are standing bunches 5–8 cm long in the axils of the leaves or on side shoots.

Fruits, in short sprays, are round or wider than long, up to 1.3 cm broad, and 1 seeded. They taste intensely bitter.

The wood is heavy, hard, strong and red brown coloured [1].
Preferentially *Prunus africana* grows at a level of 1,000 to 2,500 m in the mountain forests of West Africa (Ghana, Cameroon), East Africa (Ethiopia, Kenya, Uganda, Tanzania, Eastern Congo and Madagascar). It also occurs in Southern Africa.

In the last decade, the annual harvest of *Prunus africana* has significantly increased; for this reason trade in its bark has been added to Appendix II of the Convention in Trade in Endangered Species (CITES). Meanwhile a sustainable cultivation and harvest of the bark has been introduced in Cameroon [2].
Fig. 1: Pygeum africanum (*Prunus africana*).
2.2 Historic Use
The bark has been utilised, presumably since ancient times, for medicinal purposes in South Africa and other African countries. An infusion of powdered bark in milk or water is a tribal remedy for the treatment of bladder pain and micturition problems.

2.3 Chemistry of Pygeum africanum Bark
Pygeum africanum contains several groups of substances, identified and quantified according to modern scientific analytical methods. The most important constituents of the bark are triterpenes, saturated and unsaturated fatty alcohols and acids and their esters.

Figure 2 shows some plant compounds contained in the bark.
The following table gives a general review of the substances found in Pygeum africanum bark.
Tab. 2: Substances found in *Prunus africana* bark (3, 44, 5, 6, 8)

<table>
<thead>
<tr>
<th>Active and Other Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phytosterols:</strong></td>
</tr>
<tr>
<td>• β-sitosterol</td>
</tr>
<tr>
<td>• β-sitosteryl glucoside</td>
</tr>
<tr>
<td>• β-sitosterone</td>
</tr>
<tr>
<td><strong>Saturated and unsaturated fatty acids (C\textsubscript{12}-C\textsubscript{22}):</strong></td>
</tr>
<tr>
<td>erucic acid, behenic acid, linolenic acid, arachidic acid, linoleic acid, nonadecanoic acid, stearic acid, heptadecanoic acid, margaric acid, palmitoleic acid, palmitic acid, pentadecanoic acid, myristic acid, lauric acid</td>
</tr>
<tr>
<td><strong>Pentacyclic triterpenoids: ursolic acid, 2α-hydroxyursolic acid, oleanolic acid, crataegolic acid and friedelin</strong></td>
</tr>
<tr>
<td><strong>Alcohols:</strong> n-tetracosanol, n-docosanol</td>
</tr>
<tr>
<td><strong>Carbohydrates:</strong> Triacontane (C\textsubscript{30}H\textsubscript{62}), Nonacosane (C\textsubscript{29}H\textsubscript{60})</td>
</tr>
<tr>
<td><strong>Anthocyanidins</strong></td>
</tr>
</tbody>
</table>
2.4 Preparation of the Extract and Quality Control

The plant material used for Pygeum africanum extract grows in African forests. EUROMED selects carefully the dried bark of Cameroon origin, which has shown a proven activity, in comparison to other origins of the African continent, to produce a high quality.

When the plant material arrives at EUROMED an exhaustive inspection of the raw material according to the current methods guarantees the quality of the final product.

Furthermore EUROMED evaluates the possible contamination of the drug. In doing so the company assures that the limits fixed by international standards or literature are not exceeded.
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Aflatoxins: the contamination with these mycotoxins is controlled by legal limits world-wide

Heavy metals: the contamination with heavy metals is controlled by atomic absorption spectrophotometry

Microbiology: in compliance with the limits established in Ph. Eur. 3rd ed., 5.1.4 (category 4B), (1997)

![Standard thin layer chromatogram of Pygeum africanum lipidic extract from EUROMED.](image)

Fig. 3: Standard thin layer chromatogram of Pygeum africanum lipidic extract from EUROMED.

Only high-quality raw plant material, selected according to the strictest criteria, is used.

**Unique extraction process**

EUROMED applies a unique extraction process to obtain the extract. This procedure provides a high yield of valuable constituents and a high-grade extract in a careful way.
According to the original processes, Euromed produces a lipidic extract from the fruits of Pygeum africanum:

**Pygeum africanum Sterolic Lipid Extract**

Lipidic extract, viscous paste, brown colour and characteristic smell of the drug.

Euromed Pygeum extract satisfies the highest quality standards of the various European regulatory systems. It meets and exceeds all European requirements for approved European medicinal use.
2.5 Standardization

The consistent batch to batch quality of the **EUROMED** Pygeum africanum extract is guaranteed by the standardized production process. The **EUROMED** extract of Pygeum africanum bark is standardized to a content of no less than 13% of total sterols.

The analytical specifications of the **EUROMED** Pygeum africanum extract are:

- **Aspect** Brown colour, viscous paste with characteristic odour
- **Identification** GC Fingerprint
- **Solubility** Insoluble in water, soluble in organic solvents
- **Loss on drying** Max. 3.0 %
- **Ash** Max. 0.4%
- **Assay:** Total sterols as β-sitosterol min. 13.0%
- **Microbiology:** according to Ph. Eur. 3rd ed., 5.1.4., category 3B
3 Benign Prostatic Hyperplasia (BPH)

3.1 Morphology of the Prostate and of the BPH

The prostate is a single, doughnut-shaped gland about the size of a chestnut. It is below the bladder and surrounds the urethra [7] (see Fig. 4).

![Fig. 4: Profile of the urinary bladder and the prostate.](image)

Benign Prostatic Hyperplasia (BPH) develops primarily in those parts of the prostate directly adjacent to the urethra. Unlike this, carcinoma of the prostate develops mainly in the peripheral parts of the gland [8].
The proliferation of glandular and stroma cells in the periurethral and transitional zones increases after the 50th year of a man’s life (Fig. 5). The glandular nodes in the transitional zone have a increased tendency to grow with advancing years [9, 10].

![Diagram of prostate development phases](image)

**Fig. 5:** Cross and longitudinal sections of the developmental phases of the BPH.

The expanded central part of the prostate spreads to the bladder, which responds to the increased resistance with a hypertrophy of the detrusor. Later residual urine and vesicorenal reflux result in dilatation of the upper urinary tract. On a long-term basis hydronephrosis, affections of the renal parenchyma and renal insufficiency may develop.
3.2 Epidemiology

More than 50 per cent of men over 50 years and 80 per cent of men over 70 years suffer from Benign Prostatic Hyperplasia (BPH). Fig. 6 shows the incidence of BPH in relation to age. Hence BPH is the most frequent urologic disease of the aging man [11, 12, 13, 14]. It is a worldwide disease [15]. Racial, genetic and environmental influences seem to be responsible for the worldwide variance of incidence [16].

![Fig. 6: The percentage of BPH in the male population.](image)

BPH is a worldwide disease

The growing average life expectancy increases the need for therapy, since more and more patients reach the symptomatic stage of the disease [10].
3.2 Endocrinology

Development, growth and functional differentiation of the prostate are endocrinically controlled. They are influenced by the hypothalamus-hypophysis-gonads axis [17]. The excretion of gonadotrophin-releasing hormones (GnRH) from the hypothalamus stimulates the release of other hormones. Subsequently the Leydig-interstitial cells of the testicles are activated to synthesize and to secrete testosterone. In the prostatic cell testosterone is converted into dihydrotestosterone (DHT) by the enzyme 5-α-reductase. DHT has an affinity for the androgen receptors 3 to 10 times higher than testosterone. Growth and maturation of the prostate are controlled via androgen receptors [18].

The etiology is not yet clear, but there are indications that a hormonal imbalance may be involved [20]. Fig. 7 shows the androgenic aspect of the BPH genesis as well as the possible points of action of Pygeum africanum bark extract (e. g. as available from [EUROMED]).
Testosterone is metabolized into estrogens stimulating the growth of the fibromuscular tissue of the prostate [21]. In a man growing older the estrogen-androgen ratio changes in favour of the estrogens. Consequently two preconditions for BPH to arise are:
- No reduction of the male gonad function
- An advanced age of the patient.
DHT plays a crucial part in the pathogenesis of the BPH [18]: The activity of 5-α-reductase is increased in the hyperplastic prostatic tissue. That’s why more DHT is produced [15]. DHT binds to the androgen receptors and induces the biosynthesis of protein and the growth of the prostate.

Prostaglandins and leukotrienes can also contribute as mediators to the development of the BPH. In addition to their inflammatory characteristics and their ability to induce edemas they also lead to an increased cellular proliferation [15].

3.4 Symptoms

Initially symptoms affect the patient’s lifestyle. They consist primarily of unwanted change in urination. Later symptoms of increased urinary obstruction occur as disease progresses [22, 23].

The irritative symptoms are assumed to be induced by an instability of the bladder detrusor. The obstructive symptoms are caused by an exclusively mechanical stricture of the urethra (Table 3).
Tab. 3: BPH Symptoms [10, 22, 7, 15, 14].

<table>
<thead>
<tr>
<th>Irritative Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nocturia (frequent nocturnal urination)</td>
</tr>
<tr>
<td>• Pollakisuria (frequent diurnal urination)</td>
</tr>
<tr>
<td>• Urinary urgency</td>
</tr>
<tr>
<td>• Incontinence</td>
</tr>
<tr>
<td>• Feeling of incomplete voiding of urine</td>
</tr>
<tr>
<td>• Dysuria (difficulty and pain in urination)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Obstructive Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Weakened urinary stream</td>
</tr>
<tr>
<td>• Urinary stammering</td>
</tr>
<tr>
<td>• Ischuria (urinary retention)</td>
</tr>
<tr>
<td>• Terminal dribbling of urine</td>
</tr>
<tr>
<td>• Formation of residual urine in the bladder</td>
</tr>
<tr>
<td>• Delayed micturition start</td>
</tr>
</tbody>
</table>

The symptoms can cause a strong emotional crisis and affect the general condition as well as the quality of life of the patients considerably [23, 24].
Frequently it is the acute urinary retention, which causes the patient to consult an urologist. An acute erythrocyturia (blood in the urine) may make the matter more complicated.

### 3.5 Stages

The classification according to Vahlensieck [25] comprises four clinical stages of the BPH:

Tab. 4: Stages of prostatic hyperplasia.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage I</strong></td>
<td>No voiding disorder of the bladder</td>
</tr>
<tr>
<td></td>
<td>- More or less developed BPH</td>
</tr>
<tr>
<td></td>
<td>- Urinary outflow more than 15 ml/s</td>
</tr>
<tr>
<td></td>
<td>- No residual urine</td>
</tr>
<tr>
<td></td>
<td>- No trabecular bladder</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td>Changing voiding disorder of the bladder (Frequency and strength of the urinary streams)</td>
</tr>
<tr>
<td></td>
<td>- More or less developed BPH</td>
</tr>
<tr>
<td></td>
<td>- Urinary outflow between 10 and 15 ml/s</td>
</tr>
<tr>
<td></td>
<td>- No or only little residual urine (up to 50 ml)</td>
</tr>
<tr>
<td></td>
<td>- No or beginning trabecular bladder</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td></td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Steady voiding disorders of the bladder (Frequency and strength)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• More or less developed BPH</td>
</tr>
<tr>
<td>• Urinary outflow less than 10 ml/s</td>
</tr>
<tr>
<td>• Residual urine more than 50 ml</td>
</tr>
<tr>
<td>• Trabecular bladder</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady voiding disorders of the bladder</td>
</tr>
<tr>
<td>• More or less developed BPH</td>
</tr>
<tr>
<td>• Urinary outflow less than 10 ml/s</td>
</tr>
<tr>
<td>• Residual urine more than 100 ml</td>
</tr>
<tr>
<td>• Dilated bladder</td>
</tr>
<tr>
<td>• Urinary stasis of the upper urinary tract</td>
</tr>
</tbody>
</table>

A clinical interpretation of the symptoms and findings of the BPH in three clinical stages is also of general international use. This method is preferred in the Anglo-Saxon countries [26]:

- In stage I (irritation, compensatory stage) the bladder can be voided without residual urine and with normal or slightly weakened urinary stream. Urinary urgency, pollakisuria and nocturia may occur.

- Increasingly obstructive symptoms and the formation of residual urine up to about 10 ml characterize stage II (stage of beginning decompensation).
In stage III (stage of decompensation) the increasing amounts of residual urine lead to overflow incontinence. Later hydroureteronephroses with chronic postrenal kidney insufficiency may develop.

3.6 Therapy

In Stage IV, according to VAHLENSIECK, resection or ectomy is frequently the treatment method chosen, but in the Stages II and III (according to VAHLENSIECK, and I or II according to the international classification, resp.) a conservative medicamentous treatment is preferred [24].

Today conservative BPH therapy has obtained a high rank. Micturition difficulties and the formation of residual urine decrease in 60 to 70 per cent of the patients [27].

To-date mainly estrogens, gestagens and antiandrogens have been used. Recently 5-α-reductase inhibitors and the antagonists of the α1-receptors have been used. However, the rank of these medications in BPH therapy has not been finally identified [11].
Phytopharmaceutical agents have been used successfully for a long period of time. Use of these agents has seen resurgence due to the emergence of additional data regarding their mechanisms of action and clinical application [24].

Among all the mechanisms discussed, phytosterols are considered as active and have been found in experimental as well as in clinical investigations to interfere with either reduction of testosterone to dihydrotestosterone, the sex-hormone binding globulin or aromatisation of testosterone. Additional effects are documented in experiments indicating immunomodulation and anti-inflammatory qualities [20].

Having a great share of the European herbal prostatic drug market, Pygeum africanum products (as available from EUROMED) are one of the most prescribed and sold OTC preparations in Europe. Clinical tests conducted have boosted Pygeum preparations to a predominant place among all the herbal prostatic drugs [14].

The available surgical procedures are the open adenectomy, the transurethral resection (TUR-P) and the bladder incision [22]. This surgery is associated with complications and can aggravate the matter. That’s why it should be avoided unless absolutely necessary [7].
Because of their unfavourable benefit-risk ratio the TUR-P is not the therapy chosen by patients having irritative symptoms or slight to moderately severe obstructive complaints. First the application of a phytopharmaceutical agent (e.g. A Pygeum extract as available from EUROMED) should be taken into consideration [11].
In the stages I and II (international) [26] or II and III according to VAHLENSIECK [25] the conservative therapy is preferred today. The necessity of a preventive treatment in stage I is still being discussed.
4 Pharmacology

4.1 Pharmacodynamics of Pygeum Extract

Many different mechanisms account for efficacy

The therapeutic benefit of Pygeum extract (e.g. as available from EUROMED) in treating micturition symptoms of BPH is not yet fully determined. The extract of Pygeum has, due to its different constituents, several sites of action.

4.1.1 Effect on Bladder Contractility

Reduction of the bladder hypercontractility

Age related hypercontractility of the bladder in rats is reduced by long term application of Pygeum africanum extract. The sensitivity of the bladder to electrical stimulation, phenylephrine, adenosine triphosphate and carbachol is also reduced [28, 29]. This effect is not due to anticholinergic activity, as Prunus africana does not antagonize neither the in vitro action of acetylcholine on isolated rabbit detrusor muscle nor the in vivo action of oxotremorine in the mouse [29].
4.1.2 Anti-inflammatory Activity

Inflammatory cell infiltration seems to play an important role in BPH. Inhibitory effects of Pygeum africanum extract on the production of chemotactic leukotrienes and other 5-lipoxygenase metabolites, tested with in vitro preparation of human polymorphonuclear cells stimulated with calcium ionophore A23187, may account at least in part for its beneficial effect in this pathology [30, 31, 32].

Fig. 8: Arachidonic-acid cascade and point of impact of Pygeum africanum extract.
4.1.3 Inhibition of Fibroblast Proliferation

Extracts of Pygeum africanum bark (as available from [EUROMED]) have a potent inhibitory effect on rat prostatic fibroblast proliferation [33]. This is shown by the response to direct activators of protein kinase c (PKC), the defined growth factors bFGF, EGF and IGF-I, and the complex mixture of mitogenes in serum [35]. Effects observed by Pygeum africanum bark are suggested, at least partially, to be related to effects on PKC mediated pathways. Antiproliferative effects of Pygeum africanum extract were dose dependent and not ascribed to cytotoxicity. Results suggest that therapeutic effects could be, at least in part, due to the inhibition of growth factors involved in prostatic overgrowth in man [34, 35].

4.1.4 Effect on Adrenal Androgens

IK.2 (Docosanol) shows an increased adrenal androgen secretion in rats leading to a stimulation of the prostate. This effect was particularly evident in orchiectomized animals. It was concluded that an influence of adrenal steroids on epithelium and stroma of the enlarged prostate may be of clinical relevance in BPH [36, 37].
4.1.5 Effect on 5-α-reductase and Aromatase

Two of the most important enzymes involved in BPH, 5-α-reductase and aromatase, were inhibited by an extract of *Prunus africana*. It was demonstrated in vitro that an extract of *Prunus africana* showed an inhibition of 5-α-reductase with an ED$_{50}$ calculated as 0.78 mg/ml [38]. Also aromatase was inhibited at an ED$_{50}$ calculated as 0.98 mg/ml. Both effects are concentration dependent.

4.2 Pharmacokinetics

The extract of Pygeum africanum (as available from EUROMED) is a complex compound. Therefore pharmacokinetic experiments are difficult and, due to the different sites of action, at the moment they are not available.
5 Toxicology

The toxicity of Pygeum africanum extract (as available from ...) is generally very low.

Acute Toxicity
Application of single doses up to 8g/kg in 2 rodent species (mice and rat) gave a safety coefficient, compared to the therapeutic dose of the order of 3000 [39].

Subacute Toxicity / Chronic Toxicology
High doses of Pygeum extract were orally given to rats and dogs for 1 month and 6 months (short and long term application, respectively). These doses were up to the maximum dose which could be administered (375 mg/kg/d in dogs and 750 mg/kg/d in rats, equivalent to 250 and 560 times the therapeutical dose respectively). No adverse effects were observed on hematological, biochemical and anatomic/pathologic parameters [39].

Reproduction Toxicology
Pygeum extract (80 mg/kg/d, i.e. 50 times over the therapeutical dose) had no effect on the fertility of rats [39].
Genotoxicity/Carcinogenicity

In vitro and in vivo mutagenicity studies showed a complete absence of mutagenic or clastogenic potential [39].
6 Clinical Pharmacology
Due to the complexity of Pygeum africanum extract, no data on clinical pharmacology is available.
7 Proof of Clinical Efficacy

Pygeum africanum extract (as available from EUROMED) is used for the treatment of BPH, mostly in combination with other plant products like Urtica or Serenoa extracts. For this reason most of the available clinical studies have been done with such commercial products and just a few of them use Prunus africana alone.

7.1 Clinical Trials with Placebos

Several clinical tests were conducted to study the efficacy of Pygeum africanum extract (as available from EUROMED) in treating BPH. Pygeum extract led to a reduction of the subjective micturition symptoms, improved the urinary outflow and reduced the residual urine volume.

Controlled double-blind studies have demonstrated that the extract of the bark, standardized to contain not less than 13% of total sterols as β-sitosterol, is effective in relieving all the major symptoms of BPH, including increased night-time urinary frequency, the most bothersome complaint.
In a placebo-controlled study, 120 BPH patients were given Pygeum bark extract or a placebo for 6 weeks [40]. The daily dose was 2 x 100 mg of the extract or placebo. The proband group was significantly better with respect to all the subjective and objective parameters than the control group. The results are given in Table 5.

Tab. 5: Improvement of the symptoms during Pygeum extract and placebo therapies

<table>
<thead>
<tr>
<th>Symptoms improved</th>
<th>Placebo (%)</th>
<th>Pygeum africanum (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal frequency</td>
<td>50</td>
<td>78.6</td>
<td>1%&gt;p&gt;1%</td>
</tr>
<tr>
<td>Weakening of urinary flow</td>
<td>33</td>
<td>50</td>
<td>p=0.07</td>
</tr>
<tr>
<td>Diurnal frequency</td>
<td>32</td>
<td>45</td>
<td>NS</td>
</tr>
<tr>
<td>Delay in urinary flow</td>
<td>25.6</td>
<td>55.3</td>
<td>1%&gt;p&gt;1%</td>
</tr>
<tr>
<td>Sensation of incomplete micturition</td>
<td>35</td>
<td>65.6</td>
<td>1%&gt;p&gt;1%</td>
</tr>
<tr>
<td>Terminal dripping</td>
<td>44.1</td>
<td>39.4</td>
<td>NS</td>
</tr>
</tbody>
</table>
Another study showed that the treatment of benign prostatic hypertrophy with Pygeum extract (e. g. as available from EUROMED) was effective with results similar to the previous trial. 40 BPH patients were given Pygeum bark extract or a placebo for eight weeks [41]. The daily dose was 4 x 50 mg of the extract or placebo. As in the first study, the proband group was significantly better with respect to all the subjective and objective parameters than the control group.

Both studies show a statistic significant benefit for the patients.

7.2 Open Studies
Male genito-urinary infections have increased during the last years. Antibiotics and anti-inflammatory drugs are often unable to cure the disease because they cannot diffuse into the prostatic fluid.

In a clinical study, the efficacy of Pygeum africanum extract in male genital infections was investigated. The drug was administered alone and in association with antibiotics. The effects on sexual and reproductive disturbances were evaluated. Thirty-five patients were divided in 5 groups according to the pathology to be treated. The results showed a relief of the symptoms along with an improvement of the seminal parameters. The treatment of genital infections with Pygeum africanum extract is also reliable as adjuvant when associated with antibiotics [42].

7.3 Multicentre studies
A multicentre, randomized double-blind trial showed the efficacy of an extract of Pygeum africanum (as available from EUROMED) in the treatment of micturitional disorders due to benign prostatic hyperplasia [43]. This trial was designed as a Phase III study, including 263 patients, and was carried out in 8 centres in Germany, France and Austria. Capsules containing 50 mg of Pygeum africanum extract or placebo were administered at a dosage of 1 capsule in the morning and 1 capsule in the evening over a period of 60 days.
Evaluation was mainly based on quantitative parameters as residual urine, uroflowmetry and precise monitoring of diurnal and nocturnal pollakisuria. Treatment with lipid sterolic extract of Pygeum africanum led to clear clinical improvement. Quantitative parameters showed significant differences between the *Prunus africana* and the placebo group with respect to the therapeutic response. Characteristic subjective symptoms of micturitional disorders, which were evaluated by the patients in a qualitative manner, were also significantly improved by administration of Pygeum africanum extract.

The overall assessment at the end of the therapy was that micturition improved in 66% of the patients treated with Pygeum africanum extract, compared with an improvement of 31% in the placebo group. The difference was significant at the statistical level of $P<0.001$.  


Fig. 9: Effect of *Prunus africana* bark extract on objective urinary parameters in patients suffering from BHP. Mean values treatment (day 0) and at the end (day 60) $P < 0.025$ vs. Placebo.
Summary

The treatment with Pygeum africanum bark extract (as available from EUROMED) is an effective therapy in stages I and II (international) or II or III (according to VAHLENSIECK). Micturition complaints, urinary outflow and residual urine volume are improved. However, the size of the prostate is not measurably influenced. Pygeum extract is tolerated well with minimal side effects.

7.4 Therapeutic Safety

Pygeum extract is notable for its particularly high level of clinical safety. Most of the controlled studies report the absence of any significant side effect.

In the key study by Barlet et al. [43], among the 131 patients in the verum group, 3 were withdrawn from the study because of diarrhoea (1), constipation and dizziness (1) and visual disturbance (1). The placebo group had 1 patient with impotence and 1 with soft stools. It was reported that IK2 (Docosanol) was free of side effects even if 1 of the 50 study patients was withdrawn from treatment for a subjective feeling of restlessness, difficulty in falling asleep and nausea [44].
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