Nettle Root Extract

For the Treatment of BPH
EUROMED Herbal Extracts Series 4. NETTLE

Introduction

EUROMED is a company specialized 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, therapeutic applications on a scientific basis.

EUROMED guarantees the quality of its products by a broad phytochemical know-how.
# Table of Contents

1  *Urtica dioica* Extract: General Information  
1.1 Description  
1.2 Indications  
1.3 Extract Specification  
1.4 Dosage and Methods of Administration  
1.5 Contraindications and Interactions  
1.6 Side-Effects  
2  From Plant to Extract  
2.1 Stinging nettle (*Urtica dioica*): Botanical Data  
2.2 Historic Use  
2.3 Chemistry of *Urtica dioica* root  
2.4 Preparation of the Extract and Quality Control  
2.5 Standardization  
3  Benign Prostatic Hyperplasia (BPH)  
3.1 Morphology of the Prostate gland and of the BPH  
3.2 Epidemiology  
3.3 Endocrinology  
3.4 Symptoms  
3.5 Stages  
3.6 Therapy  
4  Pharmacology  
4.1 Pharmacodynamics  
4.1.1 Inhibition of SHBG-binding activity  
4.1.2 Inhibition of aromatase, reduction of estrogen  
4.1.3 Anti-inflammatory and immune-modulating Effects  
4.1.4 Inhibition of Na⁺ K⁺–ATPase activity  
4.1.5 Cytological studies  
4.1.6 Influence on 5-α-reductase  
4.2 Pharmacokinetics  
5  Toxicology  
6  Clinical Pharmacology  
7  Proof of Clinical Effectiveness  
7.1 Clinical Trials with Placebos  
7.2 Open studies  
7.3 Multi-center studies  
7.3 Therapeutic Safety  
8  Bibliography
1  *Urtica dioica* Extract:  
General Information

1.1 Description

The Nettle root extract is a standardized herbal extract of *Urtica dioica* (Fam. Urticaceae).

The extract of *Urtica dioica* is a herbal preventive and therapeutic agent for benign prostatic hyperplasia (BPH). It results in relief of symptoms, such as:

– pollakisuria (frequent urination),
– nocturia (frequent nocturnal urination) and
– urinary urgency.

Residual urine is reduced and urinary outflow is improved.

The *Urtica dioica* extract (as available from **EUROMED**) gives most patients some relief of symptoms within the first 30 days.

The extract of *Urtica dioica* does not interact with other drugs.

1.2 Indications

The extracts of *Urtica dioica* (as available from **EUROMED**) are used in the treatment of prostatic diseases, especially benign prostatic hypertrophy (international stages I-II, stages II-III according to VAHLENSIECK), and for the stabilization of the urodynamic of the patient.
1.3 Extract Specifications

Nettle root preparations usually contain about 115 to 460 mg *Urtica dioica* extract (as available from EUROMED).

1.4 Dosage and Methods of Administration

A daily oral dose of 300-1080 mg *Urtica dioica* extract is common practice. Table 1 (page 6) gives a survey of popular European *Urtica dioica*-preparations available on the market.

1.5 Contraindications and Interactions

There are no known contraindications to the long-term use of *Urtica dioica* extract. There are no known interactions with drugs usually prescribed.

1.6 Side-effects

*Urtica dioica* extract is generally well tolerated. Side effects are rare when the standardized extract is taken. In exceptional cases gastric complaints or skin rash may occur.
Tab. 1: European Preparations containing *Urtica dioica* extract.

<table>
<thead>
<tr>
<th>Preparation Name</th>
<th>Method of extraction</th>
<th>Content of <em>Urtica</em> Extract [mg]</th>
<th>Total Extract/day [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bazoton N</td>
<td>Methanolic</td>
<td>150</td>
<td>450-600</td>
</tr>
<tr>
<td>Bazoton uno</td>
<td>Methanolic</td>
<td>460</td>
<td>460</td>
</tr>
<tr>
<td>Hostid</td>
<td>Ethanolic</td>
<td>240</td>
<td>720-960</td>
</tr>
<tr>
<td>Prostaforton N</td>
<td>Ethanolic</td>
<td>240</td>
<td>720-960</td>
</tr>
<tr>
<td>Prostaherb N Urticae</td>
<td>Methanolic</td>
<td>161</td>
<td>483</td>
</tr>
<tr>
<td>Prostaneurin</td>
<td>Ethanolic</td>
<td>125</td>
<td>500</td>
</tr>
<tr>
<td>Prostata Stada</td>
<td>Ethanolic</td>
<td>125</td>
<td>500</td>
</tr>
<tr>
<td>Serless</td>
<td>Ethanolic</td>
<td>240</td>
<td>720</td>
</tr>
<tr>
<td>Uro-POS</td>
<td>Ethanolic</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td>Urtica APS</td>
<td>Ethanolic</td>
<td>125</td>
<td>500</td>
</tr>
<tr>
<td>Urtica plus N Kapseln</td>
<td>Ethanolic</td>
<td>270</td>
<td>540-1080</td>
</tr>
<tr>
<td>Urticaprostat uno</td>
<td>Ethanolic</td>
<td>336</td>
<td>336</td>
</tr>
<tr>
<td>Urticur</td>
<td></td>
<td>115</td>
<td>230-345</td>
</tr>
<tr>
<td>Urtipret</td>
<td>Ethanolic</td>
<td>115</td>
<td>230-345</td>
</tr>
<tr>
<td>Utk/-uno</td>
<td>Ethanolic</td>
<td>200/400</td>
<td>400</td>
</tr>
</tbody>
</table>
2 From Plant to Extract

2.1 Nettle root (*Urticae radix*):
Botanical Data

The nettle root originates from *Urtica dioica*, a plant widely distributed throughout the temperate zones of Europe, Africa, Asia, Australia and North and South America [8]. Synonyms are Common Nettle or Stinging Nettle. *Urtica dioica*, preferably growing in nitrogen-rich soil, is found in bushes, escarpments, river banks and damp woods until a height of 2000 - 3000 m [42]. Among the several species of *Urtica*, the smaller *Urtica urens* has a similar distribution.

*Urtica dioica*, covered with stinging hairs, is a plant with erect, green to purplish, square 30 – 150 cm long stems. Each sting is a very sharp, hollow spine, containing an irritant fluid. The dark green leaves are opposite, cordate at the base and finely toothed. [8]. The plant has usually either male or female, small green flowers, hence the specific name of the plant, as *dioica* means “two houses” [42, 61].

The perennial creeping roots are irregularly twisted, approximately 5 mm thick and exhibit distinct longitudinal grooves. The root is hollow in cross section and the cut surface is white [61, 8].
Fig. 1: Nettle root (*Urtica dioica*) [6]
2.2 Historic Use

Nettle has been used as a medicinal plant since ancient times. Nettle leaves were recommended by Dioscorides (1st century A.D.) and Galen (2nd century A.D.) as a diuretic and a laxative, for dog bites, gangrenous wounds, swellings, nose-bleeding, dysmenorrhea, for the treatment of spleen related illnesses, pleurisy, pneumonia, asthma, tinea and mouth sores. Pliny (1st century A.D.) praised the nettle for its hemostatic properties. During the middle age, St. Hildegard from Bingen recommended nettle seeds against stomach-ache. The nettle was regarded useful for nose-bleeding, angina pectoris, cancer, headache and in the treatment of spleen, kidney and bladder complaints [8].

The use of Urtica dioica has been well-documented and recognized continuously up to the present day. This is reflected in the European monographs, which recommend the use of nettle root to relieve urinary symptoms of BPH [21, 33].

In folk and allopathic medicine the nettle plant is widely used as a diuretic, astringent, antihaemorrhagic, expectorant, for arthritis and joint muscular rheumatism and chronic skin diseases [8].
2.3 Chemistry of *Urtica dioica*

Compounds isolated in *Urtica dioica* are scopoletin (0.002-0.01%), \(\beta\)-sitosterol and its glucoside, tannins as well as other sterol and steryl glucosides [11, 21, 33, 61]. Furthermore, phenylpropanes, including homovanillyl alcohol, polyphenols, polysaccharides and their methyl ether and lignans such as neooolivil and lignans glucosides have been detected in the drug [21]. However, there is a controversy about which of the above mentioned substances can be accounted for the clinical effectiveness of *Urtica dioica*.

Other characteristic compounds are lectins (0.1-0.2%), named UDA (*U. dioica* agglutinin), which can be divided in 6 isolectins. [62]. Plant lectins are small proteins, able to recognize and bind sugar residues. UDA is able to agglutinate erythrocytes and is thought to play a major role in the antiprostatic effect of *Urtica dioica* extract [57, 28]. The following table provides an overview of the properties of UDA.
Tab. 2 Characteristics of UDA [62, 8]

<table>
<thead>
<tr>
<th>Chemical Properties</th>
<th>UDA is considered to be an antiprostatic substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight 8.5 kDa</td>
<td></td>
</tr>
<tr>
<td>Smallest lectin ever found</td>
<td></td>
</tr>
<tr>
<td>Mixture of at least 6 isolectins</td>
<td></td>
</tr>
<tr>
<td>No carbohydrate residues</td>
<td></td>
</tr>
<tr>
<td>Protein consisting of 89 amino acids</td>
<td></td>
</tr>
<tr>
<td>Single-chained</td>
<td></td>
</tr>
<tr>
<td>Resistant to acids (0.1 N HCl, 1 N AcOH, 5% TCA)</td>
<td></td>
</tr>
<tr>
<td>Resistant up to 80°C (15 min, acetate buffer)</td>
<td></td>
</tr>
<tr>
<td>Resistant against proteinases (trypsin, chymotrypsin)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biological properties</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low specific haemagglutination activity against</td>
<td></td>
</tr>
<tr>
<td>native human red blood cells</td>
<td></td>
</tr>
<tr>
<td>trypsin-treated red blood cells</td>
<td></td>
</tr>
</tbody>
</table>
2.4 Preparation of the Extract and Quality Control

Nettle roots of *Urtica dioica* originate from wild plants growing in central and eastern Europe. From this plant, specially identified and with a standard quality, manufactures different extracts.
The harvest time is determined by its experts. Adequate size and condition of the plants are of great importance to the quality of the extract of *Urtica dioica*. The exclusively manual collection is made more difficult by the sawteeth of the nettle leaves. Subsequently the collected roots are rapidly dried.

When the plant material arrives at **EUROMED** an exhaustive inspection of the raw material is carried out according to the current methods in order to guarantee the quality of the final product.

Furthermore **EUROMED** evaluates the possible contamination of the drug. Microbiological purity and presence of heavy metals, aflatoxins and pesticide residues are routinely examined. In doing so the company assures that the limits fixed by international standards or literature are not exceeded.

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

**EUROMED** applies a unique extraction process to obtain the extract. It provides a high yield of valuable constituents and a high-grade extract in a careful way.
HERBAL EXTRACTS SERIES 4. NETTLE

According to the original processes EUROMED produces an ethanolic extract from the roots of *Urtica dioica*:

- **EXTR. URTICAE E RAD. SICCUM**
  (NETTLE ROOT DRY EXTRACT)
  Fine hygroscopic powder, brown colour.

EUROMED *Urtica dioica* extract satisfies the highest quality standards. This way it is possible to meet the requirements for an effective and safe medication.

### 2.5 Standardization

The consistent batch to batch quality of the EUROMED *Urtica dioica* extract is guaranteed by the standardized production process.

The analytical specifications of the EUROMED *Urtica dioica* extract are:

- Aspect: Fine hygroscopic powder, brown colour
- Identification: TLC (DAB)
- Loss on drying: Not more than 5.0%
- Total amino acids: Not less than 5%
- Scopoletin: Not less than 30.0 ppm
- β-sitosterol: Not less than 0.8%
- Residual solvents: Not more than 0.5%
- Microbiology: according to Ph. Eur. 3rd ed., 5.1.4., category 3B

**Consistent batch to batch quality**

**An extract of the whole drug is used.**

14
3 Benign Prostatic Hyperplasia (BPH)

3.1 Morphology of the Prostate and of the BPH

The prostate gland is a single, doughnut-shaped gland about the size of a chestnut situated below the bladder, surrounding the urethra (see Fig. 4).

Fig. 4: Profile of the urinary bladder and the prostate.

Benign Prostatic Hyperplasia (BPH) develops primarily directly adjoined to the urethra in contrast to carcinoma of the prostate gland which manifests mainly in the peripheral parts of the gland [37].

The proliferation of glandular and stroma cells in the periurethral and transitional zones increases after the age of 50 (Fig. 5). The glandular nodes in the transitional zone have an increased tendency to grow with advancing age [2].
The expanded central part of the prostate gland spreads to the bladder, which responds to the increased resistance with a hypertrophy of the detrusor muscle. Later residual urine and vesico renal reflux result in dilatation of the upper urinary tract. If the disease persists, hydronephrosis, affections of the renal parenchyma and renal insufficiency may develop [2].

3.2 Epidemiology

Symptoms of pollakisuria, nocturia and urinary urgency are frequent in elderly men and can mostly be attributed to BPH. More than 50 per cent of men over 50 years and 80 per cent of men over 70 years suffer from BPH. Fig. 6 shows the incidence of BPH in relation to age [3].
Hence BPH is the most frequent urologic disease of the aging man [1, 39, 49] and is therefore very common [38]. Racial, genetic and environmental influences seem to be responsible for the worldwide variance of incidence [7].

Fig. 6: The percentage of BPH in the male population.

The growing average life expectancy increases the need for therapy, since more and more patients reach the symptomatic stage of the disease [9].

**3.3 Endocrinology**

Development, growth and functional differentiation of the prostate gland are endocrinically controlled. They are influenced by the hypothalamus-hypophysis-gonads axis [47].
The excretion of gonadotropin-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 gland are controlled via androgen receptors [46].

The etiology is not yet clear, but there are indications that a hormonal imbalance may be involved [40]. It has been proposed that estrogen, mediated by sex-hormone binding globulin (SHBG) participated in setting the pace of prostatic growth [22]. Fig. 7 shows the androgenic aspect of the BPH genesis as well as the possible points of action of Urtica dioica extract (e. g. as available from EUROMED).
Fig. 7.: Possible action of *Urtica dioica* extract (as available from EUROMED) on BPH [55]

Testosterone is metabolized into estrogens stimulating the growth of the fibromuscular tissue of the prostate [19, 55]. The estrogen-androgen ratio in elderly man changes in favor of estrogens. Consequently two preconditions for BPH to arise are:

- advanced age of the patient
- persistent male gonad function.
DHT plays a crucial part in the pathogenesis of the BPH [46]: The activity of 5-α-reductase is increased in the hyperplastic prostatic tissue. Thus DHT production is increased [38]. DHT binds to the androgen receptors and induces the biosynthesis of protein and subsequently the growth of the prostate gland.

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 edema, they can lead to an increased cellular proliferation [38].

3.4 Symptoms

Initially irritative symptoms such as nocturia, pollakisuria and urinary urgency are directive to patient’s lifestyle. Upon progression of BPH, obstructive symptoms such as weakening of the urinary stream, urinary stammering or delayed micturition start become increasingly important [38, 39, 19]. Symptoms are described in Tab. 3.

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 (Tab. 3).
Tab. 3: BPH Symptoms [9, 17, 38].

<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 considerably affect the physical condition as well as the quality of life of those affected by BPH [20].

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 [53] comprises four clinical stages of the BPH:
Tab. 4: Stages of prostatic hyperplasia.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>No voiding disorder of the bladder</td>
<td>• More or less developed BPH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Urinary outflow more than 15 ml/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Absence of residual urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Absence of trabecular bladder</td>
</tr>
<tr>
<td>Stage II</td>
<td>Fluctuating voiding disorder of the bladder (Frequency and strength of the urinary streams)</td>
<td>• More or less developed BPH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Urinary outflow between 10 and 15 ml/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Absence or little residual urine (up to 50 ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Absence or beginning trabecular bladder</td>
</tr>
<tr>
<td>Stage III</td>
<td>Steady voiding disorders of the bladder (Frequency and strength)</td>
<td>• More or less developed BPH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Urinary outflow less than 10 ml/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Residual urine more than 50 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Trabecular bladder</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Steady voiding disorders of the bladder</td>
<td>• More or less developed BPH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Urinary outflow less than 10 ml/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Residual urine more than 100 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dilated bladder</td>
</tr>
<tr>
<td></td>
<td></td>
<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 [31]:

22
• In stage I (irritative, 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.

• Stage II (stage of beginning decompensation) is characterized by increasingly obstructive symptoms and the formation of residual urine up to about 10 ml.

• In stage III (stage of decompensation) the increasing amounts of residual urine lead to overflow incontinence and urinary stasis of the upper urinary tract, which can be followed by cystitis, pyelitis, epididymitis, bladder stones and hematuria. Later hydronephrosis with chronic postrenal renal insufficiency may develop.

3.6 Therapy

In Stage IV according to VAHLENSIECK, surgical resection or prostatectomy is the preferred method, but in the Stages II and III (according to VAHLENSIECK, and I or II according to the international classification, resp.) conservative treatment is preferred.

Nowadays conservative BPH therapy has gained more importance as micturition difficulties and the formation of residual urine decrease in 60 to 70 per cent of the patients [54].
To this day 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 role of these drugs in BPH therapy has not been finally identified [52].

Phytopharmaceutical agents have been used successfully for a long period of time. Use of these agents have seen resurgence due to the emergence of additional data regarding their mechanisms of action and clinical application.

Among all the mechanisms discussed, Urtica dioica agglutinin (UDA) is considered as the active agent in Urtica dioica with antiproliferative and immunomodulating effects [36, 26, 57]. Moreover, polysaccharides isolated from Urtica dioica extract are documented in experiments to have immunomodulatory and anti-inflammatory qualities [60].

Sterol and steryl glucosides have been shown to have an inhibitory effect on aromatase, reducing the blood level of estrogens, the sex-hormone binding globulin (SHBG). Beta-sitosterol is also known for its inhibition of prostaglandin synthesis [3].
Herbal remedies for the prostate gland have gained high importance. Having a significant market share, the herbal prostatic drugs have placed themselves definitely at the top of the prostatic drugs prescribed or sold as OTC preparations in Europe. This advantage is among others based on the low level of side-effects. As a result of experimental studies and clinical tests conducted during the last 10 years Urtica preparations have taken a predominant role among all the herbal prostatic drugs [3].

The available surgical procedures are open adenectomy, transurethral resection (TUR-P) and bladder incision [17]. Surgery is associated with complications and can even aggravate the symptoms. Therefore it should be avoided unless absolutely necessary [54].

Because of the unfavorable benefit-risk ratio the TUR-P is not the preferred therapy for patients having irritative symptoms or slight to moderately severe obstructive complaints. The administration of a phytopharmaceutical agent (e. g. a Urtica dioica extract as available from EUROMED) should be taken into consideration [1].

Presently conservative treatment is preferred for the stages I and II (international) [31] or II and III according to VAHLENSIECK [53]. The necessity of a preventive treatment in stage I is still controversial.
4 Pharmacology

4.1 Pharmacodynamic

The therapeutic benefit of *Urtica dioica* extract (as available from EUROMED) in treating micturition symptoms of BPH is essentially based on inhibition of SHBG and immune-modulating effects. New findings elucidate a contribution of the property of *Urtica dioica* extract (as available from EUROMED) to influence growth factors [58].

4.1.1 Inhibition of SHBG-binding activity

Ethanolic extracts from nettle root have an inhibitory effect on SHBG on account of their content of phytosterols. This effect is selectively developed in the prostatic tissue without influencing the concentrations of testosterone, FSH and LH in the plasma and without disordered the sex-hormone system.

SHBG binds sexual hormones such as testosterone and is involved in the pathogenesis of BPH as a growth factor. Blood levels of SHBG increase with age and it is thought that an inhibition of SHBG binding capacity would suppress the further development of BPH. It has shown that the binding capacity of SHBG on human prostate gland cells can be significantly inhibited by nettle root extract (as available from EUROMED) [45, 30, 27]. The effect was dose-dependant.
4.1.2 Inhibition of aromatase, reduction of estrogen

As changes in the androgen-estrogen ratio and the development of BPH are positively correlated, increase of estrogen is thought to play a role in BPH. Estrogen receptors have been isolated in connective tissue which is known to proliferate in presence of estrogens. Inhibitors of aromatase, the enzyme converting testosterone to 17β-estradiol can inhibit estrogen synthesis and tissue hyperplasia. In-vitro experiments showed a marked inhibition of aromatase by nettle root extract and other constituents 9-hydroxy-10-trans-12-cis-octadecadien-acetate [4, 27]. These findings were confirmed by Koch [32], who detected that aromatase was mostly inhibited by lipophilic constituents of nettle root.
4.1.3 Anti-inflammatory and Immune-modulating Effects

*Urtica dioica* extract (as available from **EUROMED**) showed an antiphlogistic effect. This can be partly explained by a strong inhibition of leucocyte elastase, an enzyme increased in inflammation and involved in connective tissue degeneration and proteolysis [32].

As it is well known that prostaglandin E and leukotrienes are increased in hyperplastic prostatic gland tissue, an anti-inflammatory effect would be useful in the treatment of BPH. A watery extract of *Urtica dioica* revealed some anti-inflammatory activity in the *in vivo* carrageenan rat paw edema model [60]. A polysaccharide fraction could be isolated which showed indomethacin-like antiphlogistic effect.

In another study polysaccharides reduced hemolysis via complement activation in a dose-dependant way [59, 62]. Lectins from *Urtica dioica* in a concentration of 500 ng/ml were also found to inhibit human lymphocyte proliferation by 532% [59].

Furthermore, lectins have been found to have an immune-modulating effect. About 75% of all patients with BPH have antibodies against prostatic tissue. Lectins isolated from nettle root can modulate proliferation of mouse and human lymphocytes at a concentration of 50 µg/ml [36, 13].
4.1.4 Inhibition of Na⁺K⁺-ATPase activity

As recent studies have pointed out, the effect of androgen is possibly not only mediated by steroid receptors but also membranous interaction. To this effect Na⁺K⁺-ATPase as a possible androgen receptor has been taken into consideration [22]. The effect of Urtica dioica extract (as available from EUROMED) on the activity of prostatic Na⁺K⁺-ATPase was measured [29].

A marked inhibition (23 – 67 %) was shown by nettle root sterols such as stigmasterol and campesterol, which leads to the conclusion that lipophilic nettle root constituents inhibit prostate gland Na⁺K⁺-ATPase and suppress prostate cell growth. A BPH model in mice showed inhibition of growth by 51 % if treated by a methanolic extract of Urtica dioica [29].

4.1.5 Cytological studies

In order to elucidate the pharmacological actions of Urtica dioica, cytological studies using a fluorescence microscope were performed [63]. Cells from normal and hyperplastic prostate gland tissue were incubated with nettle root extract and a histologically examined. A diffuse increase in fluorescence was found. Secretory granules in morphologically altered cell areas were decreased in tissue incubated by Urtica dioica extract, which is assumed to reflect a reduction of the biological activity of prostate gland epithelial cells.
In another study, epithelial granular fluorescence was present in resected prostate gland tissue of patients treated with *Urtica dioica* extract (as available from **EUROMED**), whereas other tissue samples were negative [16].

### 4.1.6 Influence on 5-α-reductase

Nettle root extract up to a concentration of 500 mg/ml did not show any effect on 5-α-reductase *in vitro*. Testosterone and dihydrotestosterone stimulated prostate gland growth was not inhibited by *Urtica dioica* extract [41].

### 4.2 Pharmacokinetics

The extract of *Nettle root* is a complex compound. Therefore pharmacokinetic experiments are difficult and only available for some of its constituents.

Uptake studies have been performed in mice which received radioactive labelled UDA (2 µg – 10 mg/animal) orally. Radioactivity has been detected in blood, stomach, gut, liver and kidneys [28]. Furthermore oral uptake and excretion of UDA has been investigated in volunteers and patients after oral administration of 20 mg, using ELISA. UDA was excreted with the feces by 30 – 50 %, whereas the total amount of UDA in the urine was less than 1 % [44].
5 Toxicology

Low toxicity

The toxicity of *Urtica dioica* extract (as available from [EUROMED](#)) is generally very low.

Acute Toxicity

The acute oral toxicity of *Urtica dioica* extract has been studied in rats. The LD$_{50}$ in rats was 1721 mg/kg body weight [10].

Chronic Toxicity

In a chronic oral toxicity study, the infusion of *Urtica dioica* extract was well tolerated until 1310 mg/kg. The clinical, hematological, biochemical and histological parameters were studied [10].

Another study showed no change in transaminases, glutathion or erythrocyte deformability after administration of 0.1 ml/rat/day during 6 weeks [43].

Reproduction Toxicology

There are no data available.

Genotoxicity/Carcinogenicity

There are no data available.
6 Clinical Pharmacology

In an open multi-center study, 253 patients with BPH were studied. The probands received 600 mg extract daily for 12 weeks. Responders and non-responders could be differentiated. Total testosterone, free testosterone, the ratio testosterone-free testosterone and total testosterone-SHBG did not change significantly. Estradiol, estrone, and SHBG were found to be significantly reduced in responders. A possible effect of *Urtica dioica* on aromatase was proposed [5].

In another study the morphological changes and activity of the prostate gland was examined in 31 patients with BPH who received 1200 mg *Urtica dioica* extract during 20 weeks. Biopsy specimens showed an enlargement of cell nucleus and in some areas a diminution of secretory granules, which can be interpreted as a reduction of activity [63].

A randomized placebo-controlled double-blind study in 50 patients suffering from stage I and II of BPH, blood levels of testosterone, SHBG were tested, after treatment with 600 mg nettle root extract for 9 weeks. SHBG decreased significantly in the treatment group, while testosterone remained equal [56]. These results were confirmed by Fischer et al. [24].

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No influence on testosterone levels

Histological signs of reduced prostate gland cell activity
Fig. 9 Significant reduction of SHBG and urinary volume [56]
7 Proof of Clinical Efficacy

7.1 Clinical Trials with Placebos

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

Several controlled double-blind studies have demonstrated that the nettle root extract is effective in relieving all the major symptoms of BPH including increased night-time urinary frequency, the most bothersome complaint.

In a controlled double-blind study 72 BPH patients in stage I and II (international) were given 600 mg *Urtica dioica* extract (as available from EUROMED) or a placebo for 6 - 8 weeks [12]. The outcome was measured by the following parameters: Urinary volume, urinary outflow (mean flow, maximum flow), miction time and residual urine. The treatment group experienced a significant improvement of micturition parameters. Mean urinary flow improved by 14%, maximal urinary flow increased from 13.8 to 15.4 ml/s. Residual urine was reduced by 40 % (from 94 to 56 ml) in patients treated with *Urtica dioica* extract, indicating a relief of obstructive symptoms. Tolerance was equally good in both groups [12].
A distinct improvement of functional disorders, urinary bladder capacity, urinary outflow and micturition periods by *Urtica dioica* extract (2 x 600 mg/d given over 9 weeks) could be demonstrated in a placebo controlled double-blind study in 50 patients with BPH stage I or II. Patients of the treatment group demonstrated a significant increase of urinary volume of 43.7 % compared to the control group. Maximal urinary flow was improved by 8.6 %. The tolerance of the *Urtica dioica* extract was good, except for mild gastrointestinal symptoms in 4 cases [56].

Improvement of pollakisuria

In an another placebo controlled double-blind study, the effect and tolerance of nettle root extract was investigated in 40 patients with BPH stage II (international classification). Patients were treated with *Urtica dioica* extract or placebo for 6 months. The criteria of efficacy were subjective symptoms such as dysuria, diurnal and night pollakisuria and objective symptoms such as urinary volume, residual-urine volume. *Urtica dioica* extract led to a significant improvement of pollakisuria from 7.4 to 6.1/ 24 hours. Nocturia was markedly reduced compared to the placebo control. Residual urine volume remained equal. SHBG concentration significantly decreased from 39.6 to 35 nmol/l. The results are shown in Fig. 10. Objective symptoms worsened in patients receiving placebo. The tolerance was evaluated as good; one patient from the treatment and 6 patients from the placebo group stopped treatment [24].
7.2 Open studies

Engelmann recently compared the effect and tolerance of a single dose of 459 mg with a dose of 150 mg of *Urtica dioica* extract three times daily over a period of three months. This double-blind multi-center study included BPH patients with a residual urinary volume over 30 ml and a maximal urinary flow under 15 ml/s. No significant difference between the treatment groups could be found, but both groups experienced significant improvement of residual urine, maximal urinary flow, mictionary volume, whereas there was no change in the size of the prostate gland [18].
An open long term study including 105 patients with BPH, residual urine after TUR-P, prostate gland congestion or chronic prostatitis, confirmed the previous findings. The clinical effect of a daily dose of 600 mg nettle root extract was studied 3 months to 2 years. There was improvement in 79, no change in 19 and worsening in 7 patients. Residual urine was reduced in 52 patients to a volume between 10 - 30 ml, urinary outflow and dysuria improved. Surgery could be avoided in many cases by long-term administration of *Urtica dioica* extract (as available from EUROMED). Treatment was well tolerated, skin allergy was observed only in 2 cases [15].

In another open study the success of conservative treatment in BPH (stage I and II) was investigated in 24 patients. Eight patients received 600 mg nettle root extract during 24 weeks and 16 patients were treated for 4 weeks. Residual urine and prostate gland volume was controlled by ultrasonography. After 4 weeks residual urine was reduced in 75%, prostate gland was reduced in size in 54% of the patients [23].

### 7.3 Multi-center studies

A multi-center clinical study on 4396 patients has confirmed the efficacy of *Urtica dioica* extract in treating BPH symptoms [25]. *Urtica dioica* extract (as available from EUROMED) was given at a dose of 2 x 600 (during the first three months) or 2 x 300 mg/d for a minimum length of 140 days.
The therapy turned out to be successful in relieving nocturia and pollakisuria in 90.6% of the patients after 6 months. Fig. 11 shows overall subjective improvement in relation to length of treatment. Urinary flow and residual urine were significantly improved as shown in Fig. 12. The administration of nettle root extract was well tolerated by 97.3% of the patients [25].

Subjective and objective improvement of BPH symptoms

Fig. 11 Improvement of nocturia and pollakisuria in relation to length of treatment [25]
Fig. 12 Mean urinary flow and residual urine [25]
These good results were confirmed by a multi-center study involving 3945 patients. Patients were divided into 4 groups depending on severity of nocturia: Less than once (group 1), 1-3 (group 2), 3-5 (group 3) more than 5 (group 4). Dictionary frequency decreased significantly in group 2 to 4 after 2 weeks of treatment with 600 mg twice daily. After 8-9 weeks, a decrease of about 50% was observed. In patients with only light symptoms (group 1), decrease by 50% was only after 16 weeks of treatment. Intolerance reactions or side-effects were not reported [48].

In another multi-center study, effect and tolerance of the administration of 600-1200 mg Urtica dioica extract to 5492 patients were examined. BPH was considered improved in 4407 patients. If the results are subdivided by stage of disease, stage I was improved in 83.2 per cent, stage II in 80.4 and stage III in 60.8 per cent. Nocturia and pollakisuria were significantly decreased in all groups. Residual urine was reduced in all patients and the mean urinary flow increased by 2.4 - 3.2 ml/s depending on age of the probands. Only 0.8 per cent of the patients stopped their participation in the study because of side-effects, mainly because of gastrointestinal complaints [51].
A prospective multi-center observational study investigated 4914 patients with micturition complaints (BPH stage I and II according to Alken). The probands received 459 mg *Urtica dioica* extract per day over a period of three months. Subjective symptoms were evaluated by I-PSS which improved by an average of 7.4 points (42 %). The life quality index also increased by 1.5 points (45.5 %). Maximal urinary flow increased by 3.3 ml/s while residual urine was shown to decrease from 58 to 33 ml. Furthermore prostate gland volume decreased by 1.9 ml, which the authors attributed to a standstill of growth [50].

**Summary**

The treatment with *Urtica dioica* extract is an effective therapy for the stages I and II (international) or II or III (according to VAHLENSECK). Micturition complaints, urinary outflow and residual urine volume improve under treatment. However, the size of the prostate gland is not measurably influenced. *Urtica dioica* extract is well tolerated.

Hence *Urtica dioica* extract (as available from SUROMED) is of great importance to phytotherapy. The evaluation of the Bundesgesundheitsamt/ Federal Public Health Department (today: Bundesinstitut für Arzneimittel und Medizinprodukte/ Federal Institute for Drugs and Medical Devices) on efficacy and harmlessness of *Urtica dioica* in treating BPH resulted in a positive monograph [33].
7.3 Therapeutic Safety

_Urtica dioica_ extract is notable for its particularly high level of clinical safety. To-date acute cases of _Urtica dioica_ extract poisoning have not been reported.

Particular emphasis should be put on the high tolerance of nettle root preparations leading to a high level of treatment compliance because of the almost total absence of side-effects.
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46


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