Black Cohosh Rhizome Extract

For the Treatment of Menopausal Complaints
**Introduction**

**EUROMED** is a company specialized in producing botanical extracts and active principles used as phytomedicines in pharmacy. **EUROMED** develops and produces therapeutically active raw materials.

For that purpose, the botanical raw materials are subject to strict selection and inspection criteria. The 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.
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1 Black Cohosh Extract:  
General Information

1.1 Description  
Black cohosh extract is a standardized herbal extract for treating menopausal complaints. It results in relief of subjective symptoms, such as:  
– hot flushes  
– outbreaks of sweating  
– restlessness  
– anxiety  
– irritability.  
Psychological as well as neurovegetative symptoms are improved.

1.2 Indications  
The extract of black cohosh manufactured by EUROMED is used for the treatment of menopausal complaints, including postoperative deficiency symptoms after ovariectomy and for the psychological and neurovegetative stabilization of the patient.

1.3 Extract Specifications  
Black cohosh preparations usually contain about 5 - 80 mg Cimicifuga racemosa extract (as available from EUROMED).
1.4 Dosage and Methods of Administration

Daily oral doses corresponding to 80 mg of the drug are common practice. According to the German Commission E monograph from 1989, Cimicifuga tablets should not be taken for a period exceeding 6 months [18], but long-term use has been recommended by several authors [1, 26, 31, 41].

Table 1 (page 6) gives a survey of the black cohosh-preparations available on the European market. Additionally, black cohosh is used in combination with other plants and in homeopathic preparations [36].

1.5 Contraindications and Interactions

There are no known contraindications to the use of black cohosh extract. Cimicifuga should not be taken during pregnancy and lactation. Taking into account the indication “menopausal complaints” this is not a factor of importance. There are no known interactions with drugs usually prescribed.

1.6 Side-effects

Black cohosh extract is generally well tolerated and the safety of the drug can be regarded as very good. Side effects are rare.
In a few cases headaches, gastrointestinal disturbances and weight problems may occur, which is not surprising as these symptoms are associated with the indications of *Cimicifuga racemosa*.

Table 1: European preparations containing black cohosh extract.

<table>
<thead>
<tr>
<th>Preparation Name</th>
<th>Method of extraction</th>
<th>Content of Black Cohosh Extract [mg]</th>
<th>Total Extract/day [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefakliman® mono</td>
<td>Ethanolic</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>CimiPure®</td>
<td>Ethanolic</td>
<td>80</td>
<td>160</td>
</tr>
<tr>
<td>Cimisan® /-T</td>
<td>Ethanolic</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Femicin®</td>
<td>Ethanolic</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Femilla® N Tinktur</td>
<td>Ethanolic</td>
<td>20 g /100 ml</td>
<td>80</td>
</tr>
<tr>
<td>Klimadynon®</td>
<td>Ethanolic</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Remifemin®</td>
<td>Ethanolic</td>
<td>1*</td>
<td>16-24</td>
</tr>
</tbody>
</table>

*calculated as 27-Deoxyactein
2 From Plant to Extract

2.1 Black cohosh (*Cimicifuga racemosa*): Botanical Data

The parent plant of black cohosh is *Actaea racemosa* (*Cimicifuga racemosa*). It is indigenous to the eastern part of North America where it is found in New England, Wisconsin and far down to the south [11, 25, 33]. Synonyms are bugbane, black snakeroot, rattlesnake root, squaw root or cohosh, as well as *Schlangenwurzel*, *Frauenwurzel* in German and *Actée à grappet* in French [1]. *Cimicifuga racemosa* grows in shady, deciduous forests and near hedges [11, 16, 25].

*Actaea racemosa*, grows up to 2 meters high and has an upright bare branched stem, very large tripartite leaves, white racemed flowers and leather-like capsules [8, 23, 35]. The seeds make a rattling noise when the wind is blowing, hence the name *rattle weed*. It has been noticed that insects, especially bugs, avoid this plant, a feature which accounts for its Latin name (lat. *cimex* = “bug” and *fuga* = “drive away”) [1].

The rhizome is cylindrical, 1 - 2.5 cm thick, up to 15 cm long and more or less branched. Rhizome and roots are dark brown with vertical furrows. In the roots the vascular bundles are arranged in a cross-like shape [16, 33].
Fig. 1: Black cohosh (Cimicifuga racemosa) [16]
2.2 Historic Use

The native Americans of Canada, Wisconsin and Missouri have used the rhizome of *Cimicifuga racemosa* for different indications such as pain during childbirth and menstruation. The fresh root was applied to rattlesnake bites [16]. The rhizome was also used to treat general malaise, kidney ailments, rheumatism and malaria, as well as bronchitis, fever, nervous and uterine disorders. *Cimicifuga racemosa* and other *Cimicifuga* species have been widely used in traditional Chinese and Japanese Medicine as antipyretic and antiphlogistic agents [33].

In 1743 the physician Colden recommended *Cimicifuga racemosa* to disperse cirrhotic ulcers and induce labor. Linné included the plant into his *Materia medica*. *Cimicifuga* was known in gynecology since the middle of the 18th century [23, 35]. During the 19th century black cohosh tincture or liquid extract was used in folk medicine as a bitter tonic, as antirheumatic and antipyretic substance, for dizziness, St. Vitus’ dance, amenorrhea, dysmenorrhea and spermatorrhea. *Cimicifuga racemosa* has also been known in homeopathy for the treatment of gynecological disorders [16, 25].

The use of black cohosh has been well-documented up to the present day. This is reflected in the monograph, which recommends the use of black cohosh to treat premenstrual, dysmenorrheal and menopausal neurovegetative symptoms [18].
At the moment the plant is mainly used for menstrual problems, disorders during puberty and menopausal complaints [11].

2.3 Chemistry of *Cimicifuga racemosa* rhizome

*Triterpene glycosides as main compounds*

The main compounds isolated in *Cimicifuga racemosa* are glycosides, namely triterpene glycosides: actein and its aglycone acetylacteol, cimicifugoside and its aglycone cimigenol, 27-deoxyactein, desoxyacetylacteol and other aglycones. Furthermore flavonoids and aromatic acids like isoferulic and salicylic acids have been isolated. In addition the rhizome contains resins, volatile oil, fatty acids, tannins, alkaloids, phytosteroles, starch and sugar (see Fig. 2) [1, 8, 11, 22, 25, 28, 33].

Recently three new cyclolanostanol xylosides were isolated from a batch of black cohosh rhizome: The cimicifugosides H-1, H-2 and H-5 [17]. Their pharmacological and clinical effects have not yet been established.

It is still not evident which of the above named components are to be accounted for the clinical effect of *Cimicifuga racemosa*. Therefore the whole extract of the rhizome is regarded as the active ingredient.
Black cohosh extract is standardized to these triterpene glycosides, calculated as 27-
desoxyactein [8, 35].

EUROMED has developed an effective technique to obtain quantitative determination of triterpene
glycosides for the routine analysis of black cohosh extracts using HPLC with evaporative
light scattering detector. Triterpene glycosides have been identified by comparison of the
retention times with reference standards isolated in EUROMED and with the data obtained with
HPLC and mass spectrometry.

The method developed by EUROMED results to be very selective, sensitive, reproducible and easy to
use for routine analysis of black cohosh extracts compared to UV/vis spectrophotometric
techniques. These techniques, usually used for the standardization of this product, are poor in
sensitivity and selectivity for the determination of triterpene glycosides and, therefore, non reliable
qualitative or quantitative data can be obtained.
2.4 Preparation of the Extract and Quality Control

The rhizome of *Cimicifuga racemosa* originates from plants grown in USA and Canada. From this plant manufactures the extract.
Adequate size and condition of the plants are of great importance to the quality of the extract of black cohosh. The collected rhizomes are rapidly dried in a dark place. The plant loses its unpleasant smell during storage.

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 checks the possible contamination of the drug. Microbiological purity and the presence of heavy metals are routinely checked. In doing so the company assures that the limits fixed by international standards or literature are not exceeded.
HERBAL EXTRACTS - BLACK COHOSH

Fig. 3: High performance liquid chromatogram of black cohosh extract from **EUROMED**

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

The **EUROMED** extraction process produces a high yield of valuable constituents and a high-grade extract (Fig. 3).

According to the original processes **EUROMED** produces a dry extract from the roots of *Cimicifuga racemosa*:

- **BLACK COHOSH DRY EXTRACT**
  
  **EXTR. CIMICIFUGAE E RHIZ. SICCUM**
  
  Fine powder, brown color, aromatic odor.
Black cohosh extract meets the highest quality standards, providing an effective and safe medication.

### 2.5 Standardization

**Steady and high quality**

The steady and high quality of the black cohosh extract is guaranteed by a standardized production process.

**An extract of the whole herb is used**

The analytical specifications of the black cohosh extract are:

- **Aspect**
  Fine hygroscopic powder, brown colour, aromatic odour

- **Identification**
  TLC (HAB), UV fingerprint

- **Loss on drying**
  Max. 5.0 %

- **Assay**
  Total triterpene glycosides as 27-deoxyactein min. 2.5% (HPLC-method)

- **Microbiology**
  Acc. Ph. Eur. 3rd ed., 5.1.4., category 3B
3 Menopausal Complaints

3.1 Epidemiology

Almost one third of the female world population is between 45 and 60 years old. An overwhelming large proportion (up to 85%) of these women suffer from menopausal symptoms. Two million women between 50 and 60 years are still employed full-time, but due to the severity of the menopausal symptoms 10 to 20% are only partly able to work, and 5% are permanently disabled. As life expectancy has grown in the industrialized countries, one third of a woman’s life comes after the menopause [21, 30, 34]. Fig. 4 shows the incidence of menopausal vegetative symptoms in relation to age (menopausal phase). Hence menopausal complaints are a large-scale problem in industrialized countries, a safe and effective treatment is needed.

Fig. 4: The vegetative menopausal syndrome during the menopause [19].
3.2 Endocrinology

Fertility is controlled by complex cyclical hormonal changes in the hypothalamic-pituitary-ovarian axis. During the menopausal phase, which lasts several years before and after the menopause, a progressive loss of gonadotropin-stimulated primary ovarian follicles is associated with a decrease of the production of estrogen and progesterone. As a result of the low estrogen level, the gonadotropin follicle stimulating hormone (FSH) and luteinizing hormone (LH) increase through the non-inhibition of the negative feedback mechanism. The endocrine situation of a menopausal woman is characterized by low estradiol and high LH-levels as shown in Fig. 5 [29, 13].

![Endocrine System Diagram](image)

**Fig. 5:** Hormonal regulation during menopause: Decreased levels of estradiol and progesterone disinhibit the LH and FSH-production.
A prerequisite for an estrogenic action is the presence of estradiol receptors. They are expressed in the hypothalamus, the pituitary gland, the follicular granulosa, the epithelium of the vagina and the endometrium of the uterus. Due to oscillating levels of LH before menopause, hypothalamic functions are unstable which is manifested by a dysregulation of the neurons regulating body temperature and the cardiovascular system, leading to hot flushes and palpitations of the heart. Low estrogen levels in the limbic system cause emotional instability [45, 34, 8]. Fig. 6 shows the hormonal imbalance during the menopause and the possible points of action of Cimicifuga racemosa extract (as available from EUROMED).

Fig. 6: Possible points of action of Black Cohosh extract (as available from EUROMED) on menopausal complaints
3.3 Symptoms of the menopausal syndrome

Menopausal symptoms can be vegetative, organic, psychological or metabolic. Table 2 gives an overview of the most important symptoms of the menopausal syndrome:

Table 2: Symptoms of the menopausal syndrome [8, 19, 29, 41, 44].

<table>
<thead>
<tr>
<th>Organic Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Menstrual disturbances: irregular and heavy menstrual bleeding</td>
</tr>
<tr>
<td>- Atrophy of skin, vaginal and urethral mukosa (vaginal dryness, pruritus genitalis and urine loss)</td>
</tr>
<tr>
<td>- Peripheral edema</td>
</tr>
<tr>
<td>- Constipation, meteorism</td>
</tr>
<tr>
<td>- Paresthesia</td>
</tr>
<tr>
<td>- Muscle, joint, bone pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vegetative Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hot flushes, sweating</td>
</tr>
<tr>
<td>- Headaches</td>
</tr>
<tr>
<td>- Dizziness, palpitations</td>
</tr>
<tr>
<td>- Sleep disturbances</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychological Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Depression, feeling of frustration and failure</td>
</tr>
<tr>
<td>- Poor concentration, forgetfulness, tiredness</td>
</tr>
<tr>
<td>- Reduced libido</td>
</tr>
<tr>
<td>- Discontentment, introversion, antisocial behavior</td>
</tr>
<tr>
<td>- Physical and mental exhaustion</td>
</tr>
<tr>
<td>- Irritability, nervousness, inner tension, anxiety, mood swings</td>
</tr>
</tbody>
</table>
Metabolic Symptoms

- Weight gain
- Hypertension, hyperlipidemia
- Osteoporosis

3.3.1 Organic symptoms

Hormonal imbalances in the premenopause lead to irregular and/or heavy menstrual bleeding, often in association with anovulatory cycles. This can cause anemia and result in a decrease in work performance. Another common complaint is vaginal dryness, which is due to the atrophy of vaginal mucosa [29].

Frequently reported organic complaints are edema of arms and legs, constipation and paresthesia [19].

3.3.2 Vegetative symptoms

Vegetative complaints are characterized by a sudden onset of an intense feeling of heat, accompanied by profuse sweating, feelings of irritation, anxiety and panic. Hot flushes occur in up to 85% of menopausal women and there is only a slow decline in incidence to 57% 10 years or more after the menopause (Fig. 7) [29].

Hot flushes are frequently associated with palpitations, feeling of tenseness, tiredness, irritability, muscle and joint pain, and depression. Therefore the frequent occurrence of hot flushes can markedly decrease the quality of life for affected women [29].
3.3.3 Psychological Symptoms

Fifty percent of the menopausal women experience mental disturbances such as depression, nervousness, insomnia and poor memory [13, 16]. Mood swings, anxiety, feeling of discontentment and failure are frequently reported by women. Though psychological symptoms are not directly linked to hormonal imbalances, they occur more frequently during the premenopause and improve with administration of estrogens [19].
3.3.4 Metabolic symptoms

Hormonal changes in the aging woman are often associated with metabolic changes. Many women notice a weight gain. Blood pressure increases and a change in the atherogenic lipoprotein pattern with a decline in high-density lipoprotein (HDL) and an increase in low-density lipoprotein (LDL) cholesterol can be detected. Hypertension and hyperlipidemia are two important risk factors for cardiovascular diseases [8, 29].

Furthermore, bone loss leads to low skeletal mass and loss of bone architecture with a high risk of bone fracture [29]. According to LEHMANN-WILLENBROCK (1990), nulliparity, smoking, lack of exercise, lean build, low intake of calcium, high consumption of coffee, alcohol and animal fats are associated with a higher risk of osteoporosis [19].

The severity of symptoms depends on constitutional and psychosocial factors, as obese women have less problems than slim women and working women less than housewives. The menopausal syndrome is even largely unknown in some cultural circles [19].
3.4 Therapy

Menopausal complaints can strongly vary in severity and there is a need for different forms of therapy. However, hormonal replacement is commonly used in menopausal women in order to relieve the vegetative menopausal syndrome. But side effects and risks should be taken into account.

The hormonal replacement-therapy of menopausal complaints consists of estriol, estradiol, conjugated estrogens, a sequential estrogen-gestagen or a gestagen monotherapy [19, 20]. Estrogen derivatives have a proliferative effect on the endometrium and are a poor regulator of the menstrual cycle, causing irregular and strong bleeding. Furthermore this therapy is associated with an increased risk of endometrial carcinoma. If estrogen is combined with gestagens, women experience a return of their menses, which is frequently undesired [21].

Gestagen monotherapy does not have enough effect on the vegetative symptoms. A combination of estrogen with an androgen is preferred when a psychotrophic effect is desired. Although this combination has a good effect on menopausal symptoms, bleeding occurs more frequently and androgenic side-effects might appear [21]. Compliance in women is not very high for hormonal substitution, as it is associated with numerous side-effects such as gastric complaints, edema, mastodynia or weight gain [8, 19].
An increasing number of women refuse to take hormone preparations. Furthermore, this treatment is contraindicated for women with acute or chronic hepatopathy, melanoma, estrogen-positive carcinoma, hypertension, poorly controlled diabetes, after deep vein thrombosis or in heavy smokers [34, 41].

Long time known phytopharmaceutical agents such as black cohosh (e.g. black cohosh extract as available from EUROMED) have gained new importance, since their effects were proven in several studies. Moreover, they are generally better tolerated than hormone preparations and the level of compliance is higher.

The positive effect of *Cimicifuga racemosa* (e.g. as available from EUROMED) has been approved by the German “Commission E” [18]. Experimental studies and clinical tests have confirmed the clinical effectiveness and safety of black cohosh preparations.
4 Pharmacology

4.1 Pharmacodynamics

The therapeutic benefit of black cohosh extract (as available from Euromed) in treating menopausal symptoms is essentially based on suppression of raised LH-levels and its estrogen-like effects. The estrogen-like action, which has been assumed, remains controversial.

The first animal experiment regarding the effect of Cimicifuga racemosa extract was carried out by Macht and Cook in 1932. They investigated the effect of diluted tincture in different organs including the uterus. Further experiments in 1944 showed the effect of Cimicifuga racemosa on ovarian activity and menstrual irregularities [11].

Further investigations of adult mice have shown that the weight of the uterus and genital blood circulation can increase with injections of Cimicifuga racemosa compared to controls [1].

4.1.1 Suppression of Raised LH-Levels

Hot flushes, the most common menopausal symptom, are closely related to high pulsatile LH-levels. Measurements of LH is therefore a suitable parameter to study the potency of plant extracts with regard to hot flushes [4, 40].
The endocrine activity of black cohosh extract was demonstrated in 16 oophorectomized Sprague-Dawley rats. As oophorectomy in adult female rats produces analogous hormone levels and an interruption of the feedback mechanism between the estrogen produced in the ovaries and the hypothalamus, it is a useful model for menopausal women.

The criterion used was the reduction in the LH serum concentration after administration of aqueous-water extract and residues of dichloromethane extraction. Blood concentrations of FSH, LH and prolactin were measured. After three days administration the LH serum concentrations were selectively reduced compared to controls. The serum concentrations of FSH and prolactin remained unchanged [14].

As LH was selectively suppressed and vaginal smears remained unchanged in this experiment, the authors could not affirm that Cimicifuga preparations are purely estrogenic [14].
Further investigations in ovariectomized rats and 110 menopausal women confirmed these results. After treatment with black cohosh extract, LH but not FSH levels were significantly (p<0.05) reduced in patients (Fig. 8). The endocrine activity of fractionated extract was determined \textit{in vivo} in oophorectomized rats. The lipophilic extract exerted a strong LH suppressive effect. The selective suppressive effect on LH but not FSH secretion was explained by the fact that FSH reacts less sensitively than LH to the estrogen negative feedback as FSH release is under control of both the steroids and inhibins, whilst the LH release is controlled by the sex steroids alone [4].

Fig. 8: Serum LH levels and serum FSH levels of menopausal women after receiving placebo (hatched bars) or treatment (black bars) with \textit{Cimicifuga racemosa} for 2 months (means + SEM; * p<0.05 vs placebo group; n = 55 women per group).
Furthermore the fractions of black cohosh extract were analyzed for their \textit{in vitro} binding capability of estrogen receptors (Fig. 9). Three fractions of the extract could be separated by chromatography. Fraction 1 and 3 correspond to estrogens and to weak estrogens respectively, whereas the effective components of fraction 2 have a clonidine-like effect. Clonidine is an agonist to $\alpha_2$-adrenergic receptors and suppresses LH secretion without binding to the estrogen receptor [13].

Fig. 9: Fractions of \textit{Cimicifuga} extract (I-1 to I-3) in relation to their LH suppressing effect (open bars, left scale) and their capacity for binding to the estrogen receptor (black bars, right scale). Veh = vehicle; TC = trichloromethan [13].

4.1.2 Estrogen-like Activity

The estrogenic effect of a test substance is characterized by the simultaneous increase in prolactin and decrease in LH serum levels in oophorectomized rats as well as local effects on vagina and uterus [14].
Studies with black cohosh extract revealed a decrease in the Menopausal Index according to KUPPERMAN (see 6.1), as well as proliferation of the vaginal epithelium and lowering of the menopausal increase in the LH-level. The experimental findings correspond to the therapeutic use in estrogen deficiency. The atrophic findings in patients in the menopausal phase are improved; this can be seen in the degree of maturation of the vaginal epithelium and in the karyopyknosis and eosinophil indices [38, 44]. All these findings have been interpreted as an estrogen-like effect.

On the other hand, recently conducted animal experiments of black cohosh extract in high doses ruled out uterotrophic or vaginotrophic effects. The effect of *Cimicifuga racemosa* extract was investigated in 215 immature NMRI/BOM mice and 47 mature ovariectomized Sprague-Dawley rats respectively [5].

There were no signs of estrogenic effects in both groups. Thus black cohosh extract does not have estrogenic effects as defined by uterine growth and vaginal cornification. The decrease of LH suppression found in other studies is discussed as an interference with neurotransmitters [5].

Furthermore, *in vitro* studies with *Cimicifuga racemosa* extract in estrogen receptor-positive breast cancer cells, unlike estrogens, did not show an increase in the proliferation rate. At higher concentrations in the presence of the butanolic fraction of black cohosh extract cell division was arrested [10, 27].
In this case, the effect of *Cimicifuga* is more related to estriol than to estradiol. Estradiol is associated with an increased risk for breast, ovarian and endometrial cancer, while estriol is associated with offering some protection against these cancers [42]. The beneficial therapeutic effects on neurovegetative and psychic symptoms observed in menopausal patients [38, 43, 44] may therefore be attributable to the synergistic action of centrally acting constituents that do not work via estrogenic mechanisms but via interactions with neurotransmitters.

### 4.1.3 Binding Mechanism

A extract of black cohosh containing substances which were able to bind to estrogen receptors, was shown to reduce serum levels of LH in ovariectomized rats.

To find out the binding ability of *Cimicifuga racemosa* compounds investigations with fractionated extracts in an *in vitro* assay of the estrogen receptor binding were conducted. The chromatographic separation of the extract resulted in at least three different endocrine active compounds. One of them was found to bind to the estradiol receptor, but not to suppress LH levels. It is probable that the LH suppressing effect is the result of synergistical effects with other active substances [15].
The estrogen receptor binds only compounds structurally related to estradiol. For immunological determinations of estradiol levels in blood radioimmunoassays are a suitable analytical tool. Extracts of black cohosh should displace estradiol not only from the estrogen receptor, but also should be able to compete with radioactive estradiol for binding sites on antibody molecules directed against estradiol. The extracts displaced dose dependently the tracer from the antigen-binding site [13, 15].

The exact underlying mechanism of these estrogen-like effects of the drug have not yet been elucidated. Lipophilic extracts of black cohosh, containing isoflavonoids like formononetine, have a similar effect to estrogen and compete for binding sites on estrogen receptors. However its relative binding affinity for estrogen receptors is only 1/100th as strong as 17-beta-estradiol [26]. Furthermore it was found that formononetine could not be detected in most extracts [39].

Black cohosh extract may contain substances which can interfere with the stimulatory or inhibitory regulation of the pituitary-gonad axis, perhaps through competitive inhibition at the hypothalamic-pituitary level.
4.1.4 General Pharmacodynamics

Various animal experiments have shown antiphlogistic and hypoglycemic effects as well as a suppression of blood pressure, reduction of contraction-power of the heart and of the pulse-beat after injection of *Cimicifuga racemosa* extract.

In female mice and rats black cohosh has strengthened the reproductive organs [1]. A resinous component, termed acteina, has exhibited a hypotensive action [1, 6].

Black cohosh extract has been reported to cause peripheral vasodilatation and an increase in peripheral blood flow, following the administration of a resinous constituent, termed acteina (500 µg/kg body-weight) to patients suffering from peripheral arterial disease [6].

Triterpene compounds of black cohosh extract have been shown to possess hypocholesterolemic activity *in vivo* and an inhibitory effect on phytahaemagglutinin-induced proliferative response *in vitro*. These activities were thought to be linked to molecular characteristics between the identified triterpenes and intermediates in cholesterol biosynthesis [28].

4.2 Pharmacokinetics

The extract of black cohosh is a complex compound. Therefore pharmacokinetic experiments are difficult and results are not yet available.
5 Toxicology

*Low toxicity*

The toxicity of black cohosh extract (as available from EUROMED) is regarded as very low.

**Acute Toxicity**

Data from systematic tests are not available. The single dose toxicity of black cohosh extract is cited as > 500 mg/kg intraperitoneally in mice and > 1000 mg/kg orally in rats [1].

**Chronic Toxicity**

In a multiple dose toxicity study, the administration of black cohosh extract was well tolerated until > 6 mg/kg in rabbits (orally) and > 10 mg/kg in mice (intraperitoneally). No clinical or histopathological finding could be observed after application of *Cimicifuga* for 6 months. The “no-effect-level” was stated as 1.8 g/kg or roughly 90 times the human therapeutic dose [1].

**Genotoxicity/Carcinogenicity**

The salmonella/microsome reversion assay (AMES test) did not reveal any mutagenic toxicity [1].
6 Efficacy

6.1 Methods

The influence of black cohosh extract on the profile of menopausal complaints has been investigated in open and controlled studies using established and validated testing procedures.

For characterizing effects on neurovegetative symptoms KUPPERMAN’s Menopausal Index has been used. This index assigns more significance to the typical menopausal complaints, such as hot flushes (occurring in 75% of the patients), initiated by elevated LH release [40], by way of a higher multiplication constant, than it does to the milder concurrent symptoms.

The resulting Menopausal Index gives an indication of the severity of the menopausal syndrome: >35 severe; 20-35 moderate; 15-20 mild. A favorable therapeutic result is indicated by an index of less than 15 [23].

For characterizing effects on psychological symptoms specific scales were used:

- The HAMILTON Anxiety Scale (HAMA) is recorded by the physician and is suitable for the assessment of anxiety states, for progress supervision and also for the efficiency assessment of psychopharmaceutic drugs [9]. The scale considers both „psychological“ and „somatic anxiety“ symptom groups.
The Self-Assessment Depression Scale (SDS), is filled out by the patient and records 20 criteria related to depression which are weighted according to the frequency of their occurrence. It is suitable for the detection and quantification of depressive moods and also for the comparison of the efficiency of various treatments.

The Profile of Mood States (POMS) is a self-evaluation scale for the patient. The strength of the psychological symptoms is measured by way of a “mood profile” in which the strength of motivation and the degree of weariness, depression and ill-humor are recorded.

For characterizing the therapeutic success the Clinical Global Impression Scale (CGI) is commonly employed to assess therapeutic success and benefit versus risk appraisal of a therapy. Before the initiation of therapy, the CGI is taken as a base-line determination of the degree of severity of the illness, and thereafter the changes under treatment are differentially assessed.
For characterizing effects on somatic symptoms the degree of proliferation and maturation of the vaginal mucosa and the caryopyknotic and eosinophilic indices are regularly used to test the effects of estrogens on the vaginal epithelium. The vaginal epithelium reacts about ten times faster to hormonal fluctuations than the endometrium [32].

Apart from the clinical studies demonstrated here many papers have been published reviewing the positive effects of black cohosh extract in cases of menopausal complaints [13, 34, 35].

6.2 Clinical Trials

Three active control efficacy studies have been performed on 200 patients with menopausal complaints. It was concluded that the *Cimicifuga racemosa* extract is just as effective but with less side effects in comparison to hormones and psychopharmaceuticals. It also demonstrates a remarkable spectrum of action on the menopausal syndrome, particularly stimulation of the vaginal mucosa, improvement of somatic parameters, decrease in the Menopausal Index and the HAMA score.

Black cohosh: safer therapy in comparison to hormones
One randomized, open study was performed with 60 patients with somatic, psychological and neurovegetative menopausal symptoms in 3 treatment groups. Twenty women received 80 mg black cohosh extract in a day, 20 were treated with 0.6 mg conjugated estrogens, and another 20 with 2 mg of diazepam a day during 12 weeks. KUPPERMAN Index and SDS were carried out at the start of therapy, and after 2, 4 and 12 weeks [44].

Overall compliance was good. Five patients dropped out (one in the Cimicifuga group, two in each of the other groups). As shown in Fig. 10 and Fig. 11, an improvement in the menopausal symptoms, especially psychological and neurovegetative symptoms, was achieved with all forms of treatment. In the somatic findings there were no differences between the treatment with Cimicifuga and estrogens. The Clinical Global Impression (CGI) was comparatively good with all three forms of therapy [44].
Fig. 10: Menopausal Index assessed in the course of treatment with Cimicifuga (λ), conjugated estrogen (○) and diazepam (■)[44].

Fig. 11: Functional cytology comparing treatment with Cimicifuga (λ, ■) vs. conjugated estrogen (○, □) [44].
STOLL (1987) performed a double-blind study on 80 women (46-58 years) with typical menopausal complaints. Thirty women were treated with 80 mg black cohosh extract, 30 with 0.625 mg conjugated estrogens per day, and 20 with placebo tablets. The parameters investigated were: KUPPERMAN Index, HAMILTON anxiety scale and the degree of maturation of the vaginal epithelium.

After three months of treatment with the black cohosh preparation all parameters had significantly improved (Fig. 12 and 13). In direct comparison with the other two treatment groups, the therapeutic efficacy of Cimicifuga racemosa extract was significantly superior. Thirteen women discontinued treatment because of lack of efficacy (12 of these were in the estrogen group, 1 in the placebo group). The compliance was rated as good in almost all cases [38].
Another open study included 60 hysterectomized patients under 40 years old. They were distributed into 4 groups and treated with estriol (1 mg/day), conjugated estrogens (1.25 mg/day), an estrogen-gestagen sequential therapy (1 tablet a day) or a black cohosh extract (80 mg).

The therapeutic effects were checked after 4, 8, 12 and 24 weeks with a modified KUPPERMAN Index (extended by somatic complaints) and measurements of the serum FSH and LH. The complaints improved in the course of treatment. No significant differences in efficacy could be established between the groups [20].
6.3 Multi-center Studies

The clinical effectiveness and good tolerance of *Cimicifuga racemosa* was demonstrated in a recently published multi-center study involving 886 women, between 46 and 55 years old, who suffered from vegetative and psychological symptoms [24].

Using the CGI scale, clinical improvement was found in 89% of all the cases after only 4 weeks of treatment. All symptoms significantly improved after 12 weeks (Fig. 14). Black cohosh extract was well tolerated. Only 8% of the women studied changed their medication after the end of the study.

![Fig. 14: Median change of symptoms after 4 and 12 weeks treatment with black cohosh extract [24].](image)

The effect of *Cimicifuga racemosa* on the menopausal symptom complex was investigated in a multi-centered open clinical study including 629 women who received 80 mg of black cohosh extract for 6 to 8 weeks.
Four weeks after the onset of therapy, a clear improvement of neurovegetative complaints such as hot flushes, profuse perspiration, headaches, vertigo and palpitations, and psychological disturbances such as irritability, sleep disturbances and depression was found in 80% of all treated women. In some of the patients the symptoms disappeared completely.

Administration of *Cimicifuga racemosa* was well tolerated with virtually no side-effects, and is therefore suitable for long-term treatment [37].

**6.4 Open studies**

An open study involving 36 women, aged 45 to 62 years, tested the effect of black cohosh on menopausal symptoms as assessed by the KUPPERMANN, and the Clinical Global Impression (CGI) Index [3]. As early as 4 weeks after the start of treatment, a highly significant decrease in the KUPPERMANN Index to < 15 and an improvement of the overall condition, as measured by the CGI, were observed (Fig. 15).

These results were confirmed by the open study of VORBERG (1984), which included 50 women who complained of neurovegetative, somatic and psychological symptoms. In 39 patients hormone treatment was contraindicated, while the remaining 11 patients refused to take hormones on principle [43].
The improvement of menopausal symptoms was assessed by the KUPPERMANN Index, the CGI and the Profile of Mood States (POMS).

![Graph showing decrease in KUPPERMANN Index values](image)

**Fig. 15:** Decrease in the sum values of the KUPPERMANN Index (weighted totals for the individual symptoms) [3]

**Improvement of psychological symptoms**

Four weeks after treatment was started, a marked decrease in the KUPPERMANN Index along with a positive CGI and an improvement of psychological symptoms such as weariness, despondency and ill-humor was noted. Furthermore, patients reported an increase in motivation and a better mood state as shown in Fig. 16 [43].
Fig. 16: Mood profile during the therapy with *Cimicifuga racemosa* [43].

Fifty women with an average age of 49 years took 80 mg of black cohosh extract per day, for 6 months. The Menopausal Index, a state of somatic, neurovegetative and psychological symptoms, and the number of hormone injections given within the observation period were evaluated [30].
Success of therapy was rated “good” to “very good” by 82% of patients.

During the six months of observation 56% of the patients did not need any further hormone injections (Fig. 17). The therapeutic success was rated by 82% of the patients as “good” to “very good”. These favorable results on menopausal symptoms, and very good patient compliance, favor the widespread use of black cohosh extract (as available from EUROMED) in women who are not willing, or able, to take hormones [30].

Fig. 17: Number of patients needing hormone injection under Cimicifuga treatment [30].

6.5 Drug Monitoring Studies

The therapeutic efficacy of Cimicifuga racemosa in cases of deficiency symptoms in the menopausal phase was analyzed by HEIZER [12]. A total of 89 women were treated 2 to 18 months, 23 of these women after radical surgery (hysterectomy including oophorectomy).
Black cohosh was extremely beneficial for the relief of vasomotor disturbances such as sweating, tiredness, insomnia and depression, without making the addition of sedatives or hormone preparations necessary.

The results were equally good in women who had undergone a radical operation during the premenopause. In the case of younger women, however, black cohosh could only slightly improve vasomotor disturbances.

Black cohosh was investigated in women with menopausal complaints and menopausal ailments, after panhysterosalpingo-oophorectomy, as well as in women with mainly vegetative symptoms and Simmond’s disease (hypopituitarism). A total of 517 women were observed for up to 4 years [2].

In 79% of patients whose ovaries were still active, it was possible to achieve an improvement with black cohosh extract alone. In patients with panhysterosalpingo-oophorectomy, the amount of hormones given could be reduced. The effect on the psychological symptoms seemed to be greater than through treatment by sex hormones.
Whether black cohosh extract was effective in treating ovarian disturbances was studied by Görlich [7]. A total of 258 women who suffered from menstrual disturbances and menopausal deficiency symptoms received black cohosh extract. The effect was reported to be excellent as long as there was not a total loss of hormone activity. The quasi-absence of troublesome hyperplastic bleeding in these women was also noted.

**Summary**

The treatment with black cohosh extract is effective for the treatment of menopausal complaints. Neurovegetative, psychological and metabolic symptoms improve under treatment. Black cohosh extract is well tolerated.

Hence black cohosh extract (as available from euromed) 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 safety of Cimicifuga racemosa in treating menopausal complaints is quoted in a positive monograph [18].
7 Therapeutic Safety

Black cohosh extract is the most used, and most studied, natural alternative to hormone replacement therapy. Good tolerability and low toxicity of the drug are very important. *Cimicifuga racemosa* (as available from [EUROMED](#)) is notable for its particularly high level of clinical safety.

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