Phytotherapy for Menopausal Complaints

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For decades, herbal drugs have been used successfully for the alleviation of climacteric complaints. Hormone therapy, on the other hand, has been questioned by recent epidemiological studies. Can phytopharmaceuticals close the therapeutic gap and can the isoflavone-rich food supplements, which are gaining in popularity, keep what advertisement promises?

The therapy of climacteric complaints with estrogens and/or estrogen-gestagen combinations is undisputedly effective and presumably mostly safe for a short therapy duration. Long-term hormone therapy (HT) for the prevention of osteoporosis, the prevention of cardiovascular illnesses and for the increase of cognitive capacities in advanced age, however, does not appear justifiable any longer in light of the results of the WHI study, which among other risks has confirmed an increased risk of breast cancer for estrogen-gestagen combinations and an increased risk of apoplexy for pure estrogen substitution. Even if the increase in the relative risk to develop a Mamma carcinoma under HT or to suffer a stroke, appears to be small; for the concerned women, however, these events have elementary and life-threatening consequences. Climacteric complaints represent a polysymptomatic clinical picture consisting of vegetative and psychical components (fig. 1). The complexity of the complaints in connection with the fact that the pharmacotherapy may have to last several months or even years in order to accompany the patient through the climacterics makes the approach of using and

Figure 1: Frequency of Climacteric Symptoms (Information in % of the patients).
Numerous herbal drugs for the therapy of climacteric complaints are known from experience medicine. In rational phytotherapy, however, exclusively extracts from the rhizome of the Black Cohosh (Cimicifuga racemosa (L.) Nutt., syn. Actaea racemosa) have been established as the only herbal drug, for which the Commission E of the former German federal health authorities has issued a positive monograph.

Black cohosh extracts are available as monopreparations and/or in combination with St John's Wort extract (Hypericum perforatum (L)). Especially climacteric patients with pronounced psychical symptoms are expected to profit from the added Hypericum.

Food Supplements

In addition to herbal drugs, increasingly food supplements on the basis of red clover (Trifolium pratense (L.), fig. 2) and soy (Glycine soja (L.), fig. 3) are advertised for the alleviation of menopausal complaints. The active compounds are the isoflavones genistein and daidzein which are released via elimination of glycosidically bound sugar residue from the substances genistin and daidzein. Additionally, the protein fractions of soy are supposed to have health supporting qualities.

In Germany, no herbal drug preparations from soy or red clover have been approved by the health authorities for the indication of climacteric complaints.

The efficacy of isoflavones is primarily derived from epidemiologic observations. In Asian cultures, whose nutrition is rich with isoflavones, fewer women suffer from climacteric complaints, and the frequency of breast cancer is also smaller than in western countries. As opposed to this, breast cancer is diagnosed with same frequency in US-Americans as in Asians who emigrated to the USA and gave up their traditional nutrition. The smaller tumor risk in Asia is attributed to soy and/or isoflavone-rich nutrition.

Recently, the tumor-protective effects have been doubted, however, more and more. Genistein, daidzein and formononetin are mild estrogen agonists, whose estrogenic activity is approximately 3 to 4 orders of magnitude lower than that of estradiol. If taken in large amounts – manufacturers recommend dosages in ranges up to two-digit milligrams – they can, however, reach levels which are by several orders of magnitude above the concentrations of the endogenous hormones in the plasma. In the presence of estradiol, they replace the natural ligand and thus can inhibit its estrogenic effect. Many cell culture experiments have shown that isoflavones inhibit the proliferation of tumor cells, as long as stronger estrogens are present. In systems lacking estrogens, however, the effect is reversed. Bodinet et al. [1] have shown that isoflavone-containing food supplements increase the proliferation of human breast cancer cells in cell culture experiments, if no natural estrogens are present. The test conditions simulate the hormone status of postmenopausal women. In animal experiments, the later occurrence of breast tumors could only be decreased, if the animals had been fed with isoflavones already before maturation. The administration at a later age had no protective effects, but sped up the growth of the tumors.
As per current know-how, the answer to the question whether isoflavones can lower the risk of specific cancers depends on the age when the isoflavones are ingested. A soy-rich diet in adolescence seems to lower the risk later, whereas administration of high doses of isoflavones in postmenopause can possibly even speed up tumor growth.

The results from studies regarding the efficacy of phytoestrogens from soy and red clover are inconsistent. In the year 2001, Sue Davis subtitled her editorial in the British Medical Journal on the subject "Phytoestrogen Therapy for Menopausal Symptoms?" with the statement: "There's no good evidence that it's any better than placebo." In 2002, Alber-tazzi concurred with this statement and admonished in [2]: "Presently, however, the use of isolated phytoestrogens in tablet form should be discouraged until efficacy and safety are satisfactorily attested." Today, carefully conducted clinical studies which prove the benefit of soy or red clover for climacteric complaints [2] are still nonexistent.

Additionally, the administration of phytoestrogens is being discussed in the context of prophylaxis of osteoporosis. The lower incidence of thigh fractures in Asians is also attributed to the consumption of phytoestrogens, however, can be explained reliably with anatomical differences, especially since the frequency of vertebra fractures is rather high in Asians. Their bone density is mostly even lower or similar to that of European women. This contradicts any bone constructive effect of phytoestrogens.

There is only a very limited number of human studies on this subject. The available data stems mostly from short-term studies with a small sample sizes which thus can merely be of orienting character. Critics doubt that the increase of the bone density observed under therapy with soy clinically, in fact, leads to a decrease in the rate of fractures. A favorable influence of isoflavones on the postmenopausal bone metabolism nevertheless may be assumed to be probable [3].

On the whole, the data on the effectiveness and safety does not appear sufficient at this time in order to be able to safely recommend phytoestrogen preparations for the alleviation of climacteric complaints or the prevention of osteoporosis.

This does, however, not decrease the nutritional value of soy by any means. There are hardly any doubts that soy proteins have health supporting qualities. Thus the FDA has confirmed already some years ago – as a result of a comprehensive evaluation of the available studies – that low-fat foods that contain at least 6.5 g soy protein per meal decrease the risk of coronary heart disease and lower the entire cholesterol level as well as the LDL level. The FDA explicitly limits this statement to intact soy protein, however, and excludes concentrated isoflavone fractions [4].

**Herbal drugs**

In Germany, the registration process clearly delineates between (herbal) drugs on the one hand and food supplements on the other. For the therapy of climacteric complaints, only preparations from the rhizome of Black Cohosh, *Cimicifuga racemosa* have been approved. The use of the *Cimicifuga-racemosa* rhizome has a long tradition. North American Indians and settlers already used Black Cohosh (Fig. 4) amongst others for the therapy of climacteric as well as general gynecological symptoms. In the last forty years, intense investigations were conducted regarding the pharmacologic and clinical effects of the Black Cohosh.

**Pharmacological effect of Cimicifuga extracts**

In the year 1985, the isoflavone formononetin was identified in a *Cimicifuga* extract. Since this discovery was unexpected for this plant, but matched the historic indications, a phytoestrogenic effect was formulated for Black Cohosh. In more recent analyses, other research groups could not verify any isoflavones in *Cimicifuga*. One needs to presume therefore that the herbal drug used for that first phytochemical investigation was contaminated.

The mode of action of Black Cohosh extracts has not been conclusively clarified to date. In the last years, however, the understanding of the pharmacological effects has been growing continuously, especially since the discovery of a second estrogen receptor subtype. Today a more differentiated consideration is possible. *Cimicifuga* therefore seems to be an estrogen receptor modulator which can act more selectively either estrogen agonistic or antagonistic depending on the target organ and the respective concentration of endogenous hormones. While in the reproductive organs no or rather anti-estrogenic effects are being observed, much speaks for (desirable) estrogen agonistic effects on the bone metabolism.

Independently of the estrogen receptor-mediated activities, compounds of *Cimicifuga* bind to different receptors in the CNS. In animal-experimental investigations, rats displayed behavior changes which seem to confirm central nervous, dopaminergic active compounds. Thereby these two theories are under no circumstances contradictory. They rather complement each other and help to understand the broad efficacy spectrum of the Black Cohosh extracts.
Clinical studies with 

Cimicifuga Preparations

In several randomized, controlled, clinical studies, the effectiveness and drug safety of Cimicifuga racemosa in daily doses of 40 to 127 mg herbal drug equivalent were examined for climacteric complaints (Tab. 1). Currently results from four placebo-controlled studies are available, which correspond to the current high-quality standards (GCP, Good Clinical Practice).

In a recently published study [5] 62 postmenopausal women were treated for 3 months with a Cimicifuga preparation, containing an ethanolic extract corresponding to 40 mg drug/day, 0.6 mg conjugated estrogens and/or a placebo-medication. The patients who received the phytopharmaceutical exhibited a decrease in the climacteric complaints comparable to estrogen. Both medications were superior to placebo. The benefit of the Black Cohosh preparation was especially pronounced for hot flushes and insomnia.

A multicentric study with 122 patients (Frei-Kleiner, 2002, Tab. 1) could show no significant difference between verum and placebo in the total group comparison; however, patients with at least moderate complaints reacted significantly better to the 12-week verum treatment. Frequency and severity of adverse events did not differ between treatment groups.

A study at Columbia University (New York) in 2001 (Jacobson et al., 2001, Tab. 1) investigated whether a Cimicifuga preparation could alleviate the climacteric complaints in breast cancer patients. The majority of the 68 study participants was additionally treated with Tamoxifen. With 40 mg herbal drug per day, the number of the hot flushes could indeed not be decreased significantly in the relatively short treatment phase; however, a significant reduction of profuse sweating was found in this especially affected collective. There were no adverse effects which would make the administration of Cimicifuga questionable in tumor patients.

The most recent and to date most extensive study [6] examined an isopropanolic extract in a larger patient collective (verum: 145, daily dose: 2 x 20 mg drug; placebo: 141) for 3 months. The validated Menopause Rating Scale (MRS I) served as proof of effectiveness. For the documentation of drug safety, adverse events and laboratory parameters were recorded. Concerning the decrease in the climacteric symptomatology, a significant superiority of the pharmaceutical could be confirmed (p = 0.0269). Especially hot flushes (p = 0.0260) and psychical complaints (p = 0.0215) decreased significantly under the therapy. In 6 patients in the verum group and 7 in the placebo group there were mild adverse events that were assessed to be at least as "possibly" connected with the medication.

These GCP-compliant clinical studies confirm a favorable benefit-risk ratio for Black Cohosh rhizome extracts. The phytopharmaceuticals do not become effective as fast as synthetic hormones do, however; the onset of effect occurs after 2 to 4 weeks.

The combination of Black Cohosh and St John’s Wort

In addition to the Cimicifuga monopreparations, a fixed combination of Black Cohosh and St John’s Wort, the latter in a dosage of approx. 300 mg drug per pharmaceutical form, has been proven effective in patients whose climacteric complaints are dominated by psychical symptoms. In a placebo controlled clinical study, 179 patients (Verum: 87; placebo: 92) with pronounced psychical complaints tried this combination [7]. The effectiveness was examined by means of a validated psychometric scale (Kupperman Menopause Index). The 6-week treatment phase revealed a significant superiority of the combination drug (p < 0.001). The psychical symptoms such as fear, lack of drive, depressive moods, nervousness and irritability improved significantly.

FIG. 4 Black Cohosh
(Cimicifuga racemosa, [Ranunculaceae])
under verum therapy (p < 0.001) and were clinically relevant, clearer than it had been recorded in other studies with only the administration Cimicifuga. The low and evenly distributed number of moderate adverse events in both medication groups confirms the good tolerability of the preparation. The safety documentation is complemented by clinical studies, which examined the interactive potential of the St John's Wort part of this preparation. There was no clinically relevant interaction between St John's Wort and the Cytochrome P450-Isoenzymes or P-Glycoprotein.

**Cimicifuga – Observations from Medical Practice**

Several comprehensive observational cohort studies, which reflect the everyday medical practice better and whose larger sample sizes make it possible to collect more reliable safety data, verify the findings gained under the restrictive conditions of controlled clinical studies. Since the late 1950s, several thousands patients have been treated in practical studies (Tab. 2).

**Table 1:** Controlled Clinical Studies with the Extract from the Rhizome of Black Cohosh

<table>
<thead>
<tr>
<th>First author (Year)</th>
<th>Patients (Study duration)</th>
<th>Medication</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Jacobson et al. (2001) [14]</td>
<td>n = 85 patients with breast cancer (2 months)</td>
<td>1. Group: n = 42; isopropanol. extract corresponds to 40 mg herbal drug/day 2. Group: n = 43; placebo</td>
<td>1. HF: C.r. = placebo (p = 0.86) 2. Reduction of profuse sweating: C.r. &gt; placebo 3. FSH; LH: no statically significant differences 4. AE: C.r. (n = 8); placebo (n = 2)</td>
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<tr>
<td>Liske et al. (2002) [15]</td>
<td>n = 152 (3/6 months)</td>
<td>Isopropanolic extract, 1. Group: n = 76; corresponds to 40 mg herbal drug/day 2. Group: n = 76; corresponds to 127 mg herbal drug/day</td>
<td>KI: clinically relevant decrease, no group difference. Response (Kupperman-Index &lt; 15): ca. 90%, vaginal cytological parameters, LH, FSH, E2, SHBG, PRL: not influenced. No serious AE.</td>
</tr>
<tr>
<td>Wuttke et al. (2003) [5]</td>
<td>n = 62 (3 months)</td>
<td>1. Group: n = 20; ethanolic extract, corresponds to 40 mg herbal drug/day 2. Group: n = 22; 0.6 mg CE 3. Group: n = 20; placebo</td>
<td>1. MRS: Reduction versus placebo: C.r. (p = 0.0506); CE (p=0.0513) 2. Bone metabolism: comparable effects for C.r. and CE 3. Endometrial thickness: C.r. not influenced, C.E. significant increase</td>
</tr>
<tr>
<td>Osmers (2004) [6]</td>
<td>n = 286 (3 months)</td>
<td>1. Group: n = 145; isopropanol. extract corresponds to 40 mg herbal drug/day 2. Group: n = 141; placebo</td>
<td>1. MRS: statistically significant superiority of C.r. versus placebo (p=0.0269) 2. Hot flushes: statistically significant superiority of C.r. versus placebo (p = 0.0260) 3. AE: C.r.: n = 50 (32 %); placebo: n = 47 (31 %) 4. No serious AE.</td>
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<tr>
<th>KI = Kupperman Menopause</th>
<th>AE Index = Adverse Events</th>
<th>C.r. = Cimicifuga racemosa</th>
<th>HAMA = Hamilton Anxiety Scale</th>
<th>MRS = Menopause Rating Scale</th>
<th>LF = Luteinizing Hormone</th>
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<tr>
<td>HF = Hot Flushes</td>
<td>CE = Conjugated estrogens</td>
<td>E2 = Estradiol</td>
<td>FSH = Follicle stimulating hormone</td>
<td>SHBG = Sex hormone binding globulin</td>
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<tr>
<td>SHBG = Sex hormone binding globulin</td>
<td>PRL = Prolactin</td>
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The two most extensive therapy studies will be described here:

704 patients with climacteric complaints participated in a multicentric observational cohort study with a fluid Black Cohosh preparation. The symptomatology improved in 75% of the women after 4 weeks already, 80% indicated a favorable influence on their symptoms after 8 weeks of therapy. 93% of the patients reported a very good tolerability. Mild and temporary concomitant symptoms occurred only in 7% of the cases and did not lead to any therapy discontinuation. The investigators did not see any relationship with the medication.

The second observational cohort study prospective included 2,228 women, who used an extract from Black Cohosh (n = 1,060) and/or a fixed combination of Black Cohosh and St John's Wort (n = 1,168) for a period of 6 months because of climacteric complaints [8]. The clinical efficacy of the preparations was assessed by means of validated psychometric test methods (MRS I; CGI). Already after a 3-month therapy even moderate to severe complaints had decreased significantly (p > 0.0001), so that their severity could be downgraded to “mild.” By the time of the final examination after 6 months of therapy, the complaints had decreased even further (p < 0.0001).

The majority of the patients did not require any further therapy.

The very good tolerability of the preparations was also confirmed in this clinical investigation. 93% of the participants stayed compliant as pre-

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**Table 2: PROSPECTIVE COHORT STUDIES WITH EXTRACTS FROM THE RHIZOME OF THE BLACK COHOSH**

<table>
<thead>
<tr>
<th>First author (Year)</th>
<th>Patients (Study duration)</th>
<th>Medication</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stolze (1982)[17]</td>
<td>n = 704 (2 months)</td>
<td>Ethanol C.r. extract, corresponding to 80 mg drug/day</td>
<td>In approx. 80% - 90% improvement of various climacteric symptoms - AE: N = 7</td>
</tr>
<tr>
<td>Daiber (1983)[18]</td>
<td>n = 36 (3 months)</td>
<td>Ethanol C.r. extract, corresponding to 80 mg drug/day</td>
<td>KI: Significant decrease (p &lt; 0,001) - AE: N = 8</td>
</tr>
<tr>
<td>Vorberg (1984)[19]</td>
<td>n = 50 (3 months)</td>
<td>Ethanol C.r. extract, corresponding to 80 mg drug/day</td>
<td>KI: Significant decrease (p &lt; 0,001) - POMS: Significant decrease (p &lt; 0,001). - AE: N = 4</td>
</tr>
<tr>
<td>Pethö (1987)[20]</td>
<td>n = 50 (6 months)</td>
<td>Isopropanolic C.r. extract corresponding to 80 mg drug/day</td>
<td>KI: Significant decrease (p &lt; 0,001), - 28 pat. (56 %) without additional hormone injection - no AE</td>
</tr>
<tr>
<td>Neßelhut and Liske (1999)[21]</td>
<td>n = 28 (3 months)</td>
<td>Isopropanolic C.r. extract corresponding to 136mg drug/day</td>
<td>Improvement of the queried climacteric symptoms (except for libido problems/urine incontinence) LH, FSH, E2, PRL: no influence Endometrial thickness: no influence. - no AE</td>
</tr>
<tr>
<td>Briese (2003) [8]</td>
<td>n = 2,228 (6 months)</td>
<td>1. Group: Isopropanolic C.r. extract, corresponding to 40 mg drug/day 2. Group: Isopropanolic C.r. extract, corresponding to 70 - 140 mg drug/day, ethanolic H.p. extract, corresponding to 600-1,200 mg drug/day</td>
<td>MRS: Statistically significant decrease in the entire symptomatology after 3 and 6 months in both treatment groups (p &lt; 0,0001) Tolerability: 1. Group: &quot;very good&quot; (54 % of the patients) 2. Group: &quot;very good&quot; (56 % of the patients)</td>
</tr>
</tbody>
</table>

KI = Menopause Kupperman index  
AE = Adverse events  
MRS = Menopause Rating Scale  
C.r. = Cimicifuga racemosa  
H.p. = Hypericum perforatum
and Tamoxifen.

Simultaneous incubation with Tamoxifen-effect occurred when there was a dose-dependent increase of the estrogenic effect of the extract, which is probably estrogen agonistic effect and rather show an anti-estrogenic tumor positive breast cancer cells disagree with an estrogen substitution as described in older literature.

Side effects ...

Cimicifuga preparations are mostly well tolerated. Intolerability and allergic skin reactions have been observed only in very rare cases [9]. As side effects occasionally "stomach complaints, possible weight gain" are mentioned. The weight gain must be seen within the context of the climacteric life stage, however. Since the metabolism slows down, as a rule, there will be weight gain with increasing age. Wing et al. [10] have recorded a mean weight gain of 2.25 kg for women between age 42 and 54.

In the last years, individual reports were published which stated that under therapy with Cimicifuga occasionally severe liver damage occurred. In the described cases, however, to some extent, other concomitant, liver-toxic drug were applied at the same time, so that a certain causality evaluation is not possible. The data from animal-experimental toxicity investigations and the clinical studies do not indicate any hepatotoxic potential, though. Nevertheless, as a cautionary measure, a reference in the patient information is recommendable.

Contraindications ...

The question whether patients who suffer or have suffered from a hormone-dependent tumor may use Cimicifuga preparations is of special importance. A decisive factor would be whether Cimicifuga has estrogen agonistic effects, as described in older literature.

Cell culture experiments with estrogen receptor positive breast cancer cells disagree with an estrogen agonistic effect and rather show an anti-estrogenic effect of the extract, which is probably supported by apoptosis-induction. In experiments with MCF-7 cells, a dose-dependent increase of the Tamoxifen-effect occurred when there was a simultaneous incubation with Cimicifuga extract and Tamoxifen.

In-vivo studies have confirmed these results. Rats with chemically induced breast tumors received 1, 10 or 100-fold the humane-therapeutic dose of an isopropanolic Black Cohosh after ovarectomy and subsequent tumor regression [11]. No tumor promotion was observed in any of the extract groups. The Cimicifuga-groups even showed a slight proliferation-inhibiting effect in comparison to the placebo medication. The histopathological examination of the animals yielded normal results. There were no other indications of an estrogen agonistic effect.

Also in clinical investigations with up to three times the recommended daily dose neither the characteristic serum parameters nor the vaginal cytology revealed any estrogen agonistic effects. This was also confirmed in the already mentioned study of Columbia University. Not only the result of the study is remarkable, but also the fact that such a study was carried out at all. If the parties responsible or the ethic committee would have had any doubts about the safety of the medication, this investigation would not have been initiated, especially, in view of the liability problems one would have had to fear in the USA.

The available data suggest that a contraindication for Cimicifuga-containing preparations in patients with hormone-dependent tumors is not justified. Also the weakening of an antiestrogenic tumor therapy, with Tamoxifen, for example, can be excluded with sufficient safety. Currently, the administration of Cimicifuga is the best and most secure therapy option for this patient collective, since a hormone substitution is contraindicated and other chemically defined pharmaceuticals mostly address only individual symptoms, and since the use of isoflavones should be discouraged because of insufficient and inconsistent data.

Outlook

Several research groups currently examine the influence of Cimicifuga on the bone metabolism. Pre-clinically it has already been possible to show that the extracts inhibited postmenopausal bone loss and support bone mineralization on several occasions [12], whereby the extracts, however, do not achieve the efficacy of Raloxifene, for instance. The above described three-armed clinical study [5] showed a comparable effect of Black Cohosh and conjugated estrogens on the bone metabolism. The “Cross laps” served as a measure for the bone degradation and the bone-specific alkaline phosphatase as a marker for the bone formation. For
the first time, an osteoprotective effect was also clinically verified, here. The results must be confirmed now in more comprehensive and longer studies, if the manufacturers strive for the approval of the licensing authorities.

Summary
In addition to hormone therapy, food supplements and phytotherapeutics are used for the treatment of the climacteric syndrome. Phytoestrogens (soy, red clover) are barely superior to placebo in the therapy of climacteric complaints, however, appear to be effective for the prevention of osteoporosis. The doubts about the safety of the isoflavone preparations increase, however. The effectiveness of Black Cohosh has been proven by controlled clinical studies. It is equal to HT and with a slower onset of its effect proves to be better tolerable than HT. There are indications of an osteoprotective effect which must be confirmed yet in further long-term studies. Cimicifuga preparations can be regarded as secure for estrogen-responsive tissue, such as breast and uterus. To patients who reject or may not use HT, therefore, an effective and well tolerable alternative is available with the Cimicifuga preparations.

Works Cited
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