Rhizoma Cimicifugae Racemosae

Definition

Rhizoma Cimicifugae Racemosae consists of the dried rhizomes and roots of *Cimicifuga racemosa* (L.) Nutt. (Ranunculaceae) (*1*)[1].

Synonyms

Actaea gyrostachya Wender, *A. orthostachya* Wender, *A. monogyna* Walt., *A. racemosa* L., *Bortrophis actaeoides* Raf., *B. serpentaria* Raf., *Christophoriana canadensis racemosa* Gouan, *Cimicifuga racemosa* (Torr) Bart., *C. serpentaria* Pursh, *Macrotis racemosa* Sweet, *M. serpentaria* Raf., *Macrotrys actaeiodes* Raf. (*4–6*).

Selected vernacular names

Actée à grappes, black cohosh, black root, black snakeroot, bugbane, bugwort, bugwort rattleroot, cimicifuga, cohosh bugbane, Frauen Wurzel, herbe aux punaises, macrotnys, macrotys, macroty's, natsushirogiku, Qatil el baq, racine d'actée à grappes, rattle root, rattle snake root, rattle top, rattleweed, rich weed, schwarze Schlangenwurzel, squaw root, squawroot, Traubensilberkerze, Wanzenkraut, zilberkaars (*7–9*).

Geographical distribution

Indigenous to eastern North America (*9*).

Description

A perennial herb, up to 1–2.5 m high; subterranean part consists of a thick, knotted rhizome system. Leaves compound, pinnate, up to 7 cm long; leaflets serrate along the margin, subcordate to subcuneate at the base. Inflorescence a long, wand-like raceme of white flowers with numerous stamens (*9*, *10*).

[1] Rhizomes and roots of *Cimicifuga heracleifolia* Kom., *C. dahurica* (Turcz.) Maxim. or *C. foetida* L. are referred to as Rhizoma Cimicifugae in the *Pharmacopoeia of the People's Republic of China* (*2*). Rhizomes and roots of *C. simplex* Warm. and related species are referred to under the same name in *The Japanese pharmacopoeia* (*3*).

Plant material of interest: dried rhizomes and roots

General appearance

Mixture of entire and broken dried rhizomes and roots. Rhizome dark-brown, hard, sub-cylindrical and somewhat knotted; 1–2.5 cm in diameter and 2–15 cm long, with numerous, closely-arranged, upright or curved branches, each terminating in the remains of a bud or a circular, cup-shaped scar; branches about 1 cm in diameter and up to 3 cm long, marked with distinct, encircling leaf scars; fracture horny; transverse surface showing a thin outer bark surrounding a ring of numerous pale, narrow wedges of vascular tissue alternating with dark medullary rays; a large central pith.

Roots attached to under surface of the rhizome or, more usually, broken off leaving circular scars. Roots dark brown, 1–3 mm in diameter, brittle, nearly cylindrical or obtusely quadrangular, longitudinally wrinkled; fracture short; transverse surface showing a distinct cambium line separating the wide outer bark from the central region composed of 3–6 wedges of lignified xylem tissue united at their apices and separated by broad, non-lignified medullary rays (*1*, *9*).

Organoleptic properties

Odour: slight; taste: slightly bitter (*1*, *9*).

Microscopic characteristics

Rhizome: yellowish-brown, suberized epidermis, several layers of starch- and resin-containing cortical parenchyma, 2 circles of open, collateral, fibrovascular bundles, the outer bundles being smaller than the inner; medullary rays separate the bundles and contain starch grains, spherical or polygonal, simple or 2–3 or even up to 6 compound; individual grains 3–15 μm in diameter with central slit-shaped hilum. Xylem contains tracheae with bordered pits and numerous strongly lignified wood fibres; and a central pith with cells resembling those of the cortex.

Root: thin epidermis, a cortex, separated into 2 zones by a distinct endodermis, and 4–6, occasionally 3, open, collateral fibrovascular bundles separated by broad, wedge-shaped medullary rays (*1*, *9*).

Powdered plant material

Light brown, odourless with a bitter taste; abundant starch grains, often occurring in masses in numerous fragments of thin-walled parenchyma; groups of small, lignified vessels with closely arranged bordered pits or, less frequently, with reticulate thickening; lignified thin-walled fibres and xylem parenchyma; fragments of brown suberized cells with thickened walls (*1*).

General identity tests

Macroscopic and microscopic and microchemical examinations (*1*, *9*), and thin-layer chromatography for the presence of characteristic flavonoids and phenolic acids (*1*, *11*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Foreign organic matter

Not more than 5% stem bases and not more than 2% other foreign matter (*1*).

Total ash

Not more than 10% (*1*).

Acid-insoluble ash

Not more than 4% (*1*).

Water-soluble extractive

Not less than 10% (*1*).

Loss on drying

Not more than 12% (*5*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests

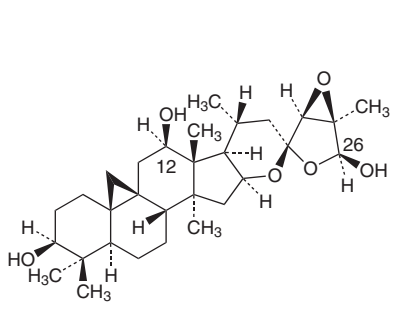
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

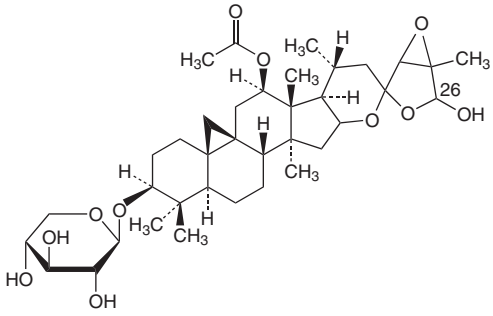
Qualitative assessments may be based on the triterpene and isoflavonoid content. Concentration ranges and quantitative methods need to be established. A high-performance liquid chromatography method is available for the quantitative analysis of flavones (*15*).

Major chemical constituents

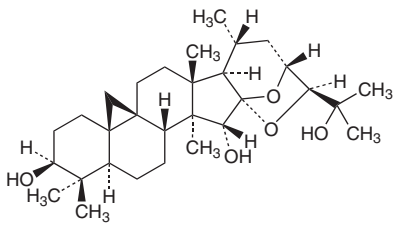
The major and characteristic constituents include the cycloartanol-based triterpenes acteol, acetylacteol, 26-deoxyacteol, cimigenol, actein, 26-deoxyactein and cimicifugoside. (*E*)-Isoferulic acid and the isoflavone formononetin are also found (*4*, *15–17*). However, the latter compound could not be detected in alcohol extracts of the root (*15*). The structures of the representative constituents are presented below.



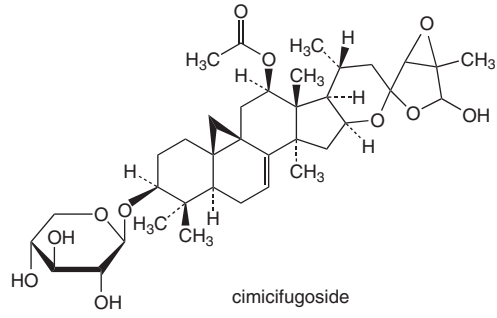
acteol



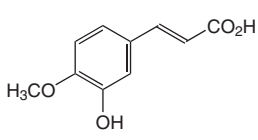
actein



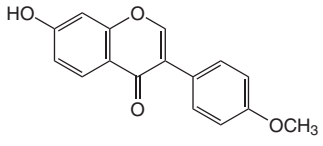
cimigenol



cimicifugoside



(*E*)-isoferulic acid



formononetin

Medicinal uses

Uses supported by clinical data

Treatment of climacteric symptoms such as hot flushes, profuse sweating, sleeping disorders and nervous irritability (*18–26*).

Uses described in pharmacopoeias and in traditional systems of medicine

Treatment of premenstrual syndrome and dysmenorrhoea (*27*, *28*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of coughs, dyspepsia, epilepsy, intercostal myalgia, rheumatoid arthritis, sciatica, snake bites, tinnitus and whooping cough (*1*, *8*, *9*, *28*, *29*).

Pharmacology

Experimental pharmacology

Estrogenic activity

The estrogenic effects of Rhizoma Cimicifugae Racemosae are controversial, and have been assessed both in vitro and in vivo. The in vitro proliferation of human mammary carcinoma cells (cell line 435) was measured after treatment with an isopropyl alcohol extract of the rhizome. Treatment using concentrations below 2.5 µg/ml did not enhance growth of the cells. However, concentrations of 2.5 µg/ml and above significantly inhibited cell proliferation (*30*). Similar results were obtained using the estrogen receptor-positive human mammary carcinoma cell line MCF-7. When these cells were treated with a 40% isopropyl alcohol extract of the rhizome at concentrations ranging from 1 ng/ml to 100 µg/ml, the extract induced a dose-dependent inhibition of cell proliferation and also augmented the antiproliferative effects of tamoxifen (*31*). An extract of the rhizome (extract not specified) was tested in vivo for possible estrogenic effects in female rats. The extract was added to a standard liquid diet and fed to ovariectomized rats daily for 3 weeks. An increase in uterine weight was observed, along with an increase in serum ceruloplasmin levels, suggesting estrogenic activity of the extract (*32*). However, in a short-term study, intragastric or subcutaneous administration of a 50% ethanol extract of the rhizome (30, 300 or 3000 mg/kg body weight) to immature mice daily for 3 days did not have any estrogenic effects, as assessed by changes in uterine weight and vaginal cytology (*33*). Constituents of a chloroform fraction, isolated from a methanol extract of the rhizome, bound to the estrogen receptors of isolated rat uteri in vitro. Formononetin, a minor constituent of the extract, showed a low binding affinity to the estrogen receptor (11.5 mmol/l) (*34*). The effects of formononetin and a dichloromethane extract of the rhizome on luteinizing hormone secretion were tested in vivo (*35*). Ovariectomized rats received nine intraperitoneal injections over 5 days (equivalent to a total

dose of 10 mg formononetin or 108 mg extract). The extract, but not formononetin, reduced the serum concentration of luteinizing hormone (*34*, *35*). Intraperitoneal (but not intragastric) administration of a chloroform (140 mg), 60% ethanol (0.3 ml) or dichloromethane (27 mg) extract of the rhizome reduced the serum concentration of luteinizing hormone in ovariectomized rats after 3–3.5 days of treatment (*34*, *36*, *37*). Serum follicle-stimulating hormone and prolactin levels, however, were not affected (*34*). Intragastric administration of a 95% ethanol extract of the rhizome (0.05 ml/animal daily) had no effect on genital functions in female mice (*38*).

The effects of estradiol on estrogen-dependent brain and uterine functions were compared with those of a dichloromethane fraction of a hydroalcoholic rhizome extract. Daily injection of the extract (60 mg/rat) or estradiol for 3 weeks reduced serum luteinizing hormone levels, but only estradiol increased uterine weight. Up-regulation of estrogen receptor-α gene expression was observed in MCF-7 mammary carcinoma cells treated with either the extract (35 µg/ml) or estradiol. The results suggest that the dichloromethane fraction of the extract may act as a selective modulator of the estrogen receptor (*39*).

Anti-inflammatory activity

Subcutaneous injection of an ethanol extract of the crude drug (100 mg/kg body weight) reduced carrageenan-induced footpad oedema in rats by 32% (*40*).

Clinical pharmacology

Climacteric symptoms

The following studies were all performed using oral administration of either a 40% isopropyl alcohol or 60% ethanol extract of Rhizoma Cimicifugae Racemosae.

In a placebo-controlled clinical trial, 110 women with climacteric symptoms were treated with the ethanol extract (8 mg daily) for 2 months. Although a significant reduction in serum luteinizing hormone levels was observed in the treated group ($P < 0.01$), there was no effect on follicle-stimulating hormone levels (*37*).

A 12-week double-blind, placebo-controlled study of 80 women (aged 45–58 years) compared the efficacy of the rhizome extract (8 mg daily) with either conjugated estrogens (0.625 mg daily) or placebo for the treatment of climacteric symptoms and vaginal atrophy. The group treated with the extract showed a greater reduction in climacteric symptoms than groups treated with either conjugated estrogens or placebo, as demonstrated by a significant reduction in both the Kupperman Index and Hamilton Rating Scale for Anxiety (Hamilton Anxiety Rating Scale), and by the proliferative status of the vaginal epithelium ($P < 0.001$) (*23*).

The efficacy of the isopropyl alcohol extract for the treatment of climacteric symptoms induced by hysterectomy was assessed in a randomized comparison trial without controls. Sixty women under the age of 40, who had

undergone a hysterectomy, but retained one ovary, were treated daily with either the extract (8 mg), estriol (1 mg), conjugated estrogens (1.25 mg) or an estrogen–progesterone combination. After 4, 8, 12 and 24 weeks of treatment, a significant decrease in climacteric symptoms was reported by the patients in all treatment groups ($P < 0.01$). This was verified by a reduction in a modified Kupperman index. Conjugated estrogens or the estrogen–progesterone combination appeared to be slightly more effective than the extract; however, no significant difference between the three treatments was observed. Serum levels of luteinizing hormone and follicle-stimulating hormone did not change significantly in any of the groups ($P > 0.05$) (*20*).

In a study without controls of 50 women with climacteric complaints, after administration of the ethanol extract (40 drops twice daily for 12 weeks), patients with moderate symptoms required no further treatment (*25*).

A randomized controlled trial involving 60 women aged 45–60 years compared the efficacy of the ethanol extract with hormone replacement therapy (0.6 mg conjugated estrogens) or 2 mg diazepam for the treatment of climacteric symptoms. Clinical assessment of the patients was based on three indicators: the menopause index (for hot flushes, nocturnal sweating, nervousness, headache and palpitations), and the Hamilton Anxiety Rating Scale and self-assessment depression scale (for psychological symptoms). Patients were treated with either the extract (40 drops twice daily), conjugated estrogens (0.625 mg daily) or diazepam (2 mg daily) for 12 weeks. All three forms of therapy reduced all three indicators. The extract and conjugated estrogens also reduced atrophic changes in the vaginal mucosa (*26*).

In a study without controls, 36 women with climacteric symptoms were treated with the ethanol extract (40 drops) twice daily for 12 weeks. A significant decrease in the average values of the Kupperman index was reported ($P < 0.001$), and an increase in the values of the Clinical Global Impression scale was observed (*18*).

A placebo-controlled clinical trial assessed the efficacy of a rhizome extract for the treatment of 82 women with climacteric symptoms. In the group treated with the extract, 31 women reported a considerable decrease in symptoms, while 10 women with severe climacteric symptoms did not show improvement. In the placebo group, a reduction of symptoms was seen in four women; symptoms were unchanged in 37 women (*19*).

In a study without controls, 50 women with climacteric symptoms, who had received at least one or two intramuscular injections of estradiol valerate (4 mg) and prasterone enantate (200 mg) during 1–2 months prior to the trial, were treated with the isopropyl alcohol extract (2 tablets twice daily) for 6 months. The therapeutic results were rated as good to very good in 41 of the patients: during the treatment period 28 required no further injections, 21 patients required one injection and one patient required two injections. The Kupperman index decreased significantly ($P < 0.001$), indicating successful treatment of symptoms (*22*).

A multicentre, drug-monitoring study without controls of 629 women with climacteric symptoms assessed the efficacy of the ethanol extract (40 drops

twice daily) for 8 weeks. Symptoms improved in over 80% of all patients after 6–8 weeks of treatment (*24*).

A 6-month randomized, double-blind clinical trial compared two different doses of the isopropyl alcohol extract (40 and 127 mg daily) in 152 women with climacteric symptoms. A decrease in the Kupperman index was observed after 2 weeks in both treatment groups. Both dosages showed similar levels of efficacy and safety. After 6 months, approximately 90% of patients had responded to the treatment. No effects on vaginal cytology or the levels of luteinizing hormone, follicle-stimulating hormone, sex hormone binding-globulin, prolactin and estradiol were observed (*21*, *41*, *42*).

A review of eight clinical trials assessed the efficacy of extracts of the crude drug for the alleviation of climacteric symptoms in women. It concluded that preparations of the rhizome may be a safe and effective alternative to estrogen replacement therapy for patients for whom the replacement therapy is contraindicated or refused (*43*).

General gynaecological disorders

Five case studies have described the successful use of a 40% isopropyl alcohol or 60% ethanol extract of the rhizome in the treatment of a total of 833 women with gynaecological disorders (e.g. climacteric symptoms) and menstrual disorders (e.g. primary or secondary amenorrhoea, and premenstrual disorders) (*44–48*).

Contraindications

Owing to its potential estrogenic effects (*39*) and the lack of data on its safety, Rhizoma Cimicifugae Racemosae should not be used during pregnancy or lactation, or in children under the age of 12 years.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

A 40% isopropyl alcohol extract of the crude drug was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 or TA100 (*16*).

Pregnancy: teratogenic effects

Intragastric administration of up to 2 g/kg body weight of the crude drug, as a component of two traditional Chinese medicines, to pregnant rats daily on days 7–17 of gestation was not teratogenic (*49*, *50*). (See also Contraindications.)

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug interactions or drug and laboratory test interactions.

Adverse reactions

Minor gastrointestinal upset and headache (*19*, *23–25*).

Dosage forms

Crude drug, and isopropyl alcohol or ethanol extracts (*16*). Store in a well-closed container, protected from light and moisture.

Posology

(Unless otherwise indicated)
Daily dosage: 40–60% isopropyl alcohol or ethanol extracts of the crude drug (*18–20*, *22–26*, *37*, *42*), corresponding to 40 mg drug (*27*).

References

1. *British herbal pharmacopoeia*. London, British Herbal Medicine Association, 1996.
2. *Pharmacopoeia of the People's Republic of China* (English ed.). Guangzhou, Guangdong Science and Technology Press, 1997.
3. *The Japanese pharmacopoeia*, 13th ed. (English ed.). Tokyo, Ministry of Health and Welfare, 1996.
4. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants*. Paris, Lavoisier, 1995.
5. Blaschek W et al., eds. *Hagers Handbuch der pharmazeutischen Praxis*. *Folgeband 2*: *Drogen A–K*, 5th ed. Berlin, Springer-Verlag, 1998.
6. Hooker JD, Jackson BD. *Index Kewensis. Vol 1*. Oxford, Clarendon Press, 1895.
7. Bedevian AK. *Illustrated polyglottic dictionary of plant names in Latin, Arabic, Armenian, English, French, German, Italian and Turkish languages*. Cairo, Argus & Papazian Press, 1936.
8. Farnsworth NR, ed. *NAPRALERT database*. Chicago, University of Illinois at Chicago, IL, February 9, 1998 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services).
9. Youngken HW. *Textbook of pharmacognosy*, 6th ed. Philadelphia, PA, Blakiston, 1950.
10. Talalaj S, Czokowicz AS. *Herbal remedies: harmful and beneficial effects*. Melbourne, Hill of Content, 1989.
11. Wagner H, Bladt S. *Plant drug analysis*, 2nd ed. Berlin, Springer-Verlag, 1996.
12. *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1998.
13. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1996.

14. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
15. Struck D, Tegtmeier M, Harnischfeger G. Flavones in extracts of *Cimicifuga racemosa*. *Planta Medica*, 1997, 63:289.
16. Beuscher N. *Cimicifuga racemosa* L.—black cohosh. *Zeitschrift für Phytotherapie*, 1995, 16:301–310.
17. Wagner H, Wiesenauer M. *Phytotherapie*. Stuttgart, Gustav Fischer Verlag, 1995.
18. Daiber W. Klimakterische Beschwerden: ohne Hormone zum Erfolg! *Ärztliche Praxis*, 1983, 35:1946–1947.
19. Földes J. Die Wirkungen eines Extraktes aus *Cimicifuga racemosa*. *Ärztliche Forschung*, 1959, 13:623–624.
20. Lehmann-Willenbrock E, Riedel HH. Klinische und endokrinologische Untersuchungen zur Therapie ovarieller Ausfallerscheinungen nach Hysterektomie unter Belassung der Adnexe. *Zentralblatt Gynäkologie*, 1988, 110:611–618.
21. Liske E, Wüstenberg P, Boblitz N. Human-pharmacological investigations during treatment of climacteric complaints with *Cimicifuga racemosa* (Remifemin®): no estrogen-like effects. In: *Proceedings of the Fifth International ESCOP Symposium*. London, European Scientific Community on Phytotherapy, 1998.
22. Pethö A. Klimakterische Beschwerden. Umstellung einer Hormonbehandlung auf ein pflanzliches Gynäkologikum möglich? *Ärztliche Praxis*, 1987, 38:1551–1553.
23. Stoll W. Phytotherapeutikum beeinflusst atrophisches Vaginalepithel: Doppelblindversuch Cimicifuga vs. Östrogenpräparat. *Therapeutikon*, 1987, 1:23–31.
24. Stolze H. Der andere Weg, klimakterische Beschwerden zu behandeln. *Gyne*, 1982, 1:14–16.
25. Vorberg G. Therapie klimakterischer Beschwerden. Erfolgreiche hormonfreie Therapie mit Remifemin®. *Zeitschrift für Allgemeinmedizin*, 1984, 60 (Suppl.):626–629.
26. Warnecke G. Influencing menopausal symptoms with a phytotherapeutic agent. *Die Medizinische Welt*, 1985, 36:871–874.
27. Blumenthal M et al., eds. *The complete German Commission E monographs*. Austin, TX, American Botanical Council, 1998.
28. Liske E. Therapeutic efficacy and safety of *Cimicifuga racemosa* for gynecological disorders. *Advances in Therapy*, 1998, 15:45–53.
29. Newall CA, Anderson LA, Phillipson JD. *Herbal medicines, a guide for healthcare professionals*. London, Pharmaceutical Press, 1996.
30. Nesselhut T et al. Untersuchungen zur proliferativen Potenz von Phytopharmaka mit östrogenähnlicher Wirkung bei Mammakarzinomzellen. *Archives of Gynecology and Obstetrics*, 1993, 253:817–818.
31. Freudenstein J, Bodinet C. Influence of an isopropanolic aqueous extract of Cimicifugae racemosae rhizoma on the proliferation of MCF-7 cells. In: *Proceedings of the Twenty-third International LOF-Symposium of Phyto-estrogens*. Ghent, 1999.
32. Elm CL et al. Medicinal botanicals: estrogenicity in rat uterus and liver. *Proceedings of the American Association for Cancer Research*, 1997, 38:293.
33. Einer-Jensen N et al. *Cimicifuga* and *Melbrosia* lack oestrogenic effects in mice and rats. *Maturitas*, 1996, 25:149–153.
34. Jarry H, Harnischfeger G, Düker E. Studies on the endocrine efficacy of the constituents of *Cimicifuga racemosa*. 2. In vitro binding of compounds to estrogen receptors. *Planta Medica*, 1985, 4:316–319.
35. Jarry H et al. Treatment of menopausal symptoms with extracts of *Cimicifuga racemosa*: in vivo and in vitro evidence for estrogenic activity. In: Loew D, Rietbrock N, eds. *Phytopharmaka in Forschung und klinischer Anwendung*. Darmstadt, Steinkopff, 1995:99–112.
36. Jarry H, Harnischfeger G. Studies on the endocrine effects of the contents of *Cimicifuga racemosa*. 1. Influence on the serum concentration of pituitary hormones in ovariectomized rats. *Planta Medica*, 1985, 1:46–49.

37. Düker EM et al. Effects of extracts from *Cimicifuga racemosa* on gonadotropin release in menopausal women and ovariectomized rats. *Planta Medica,* 1991, 57:420–424.
38. Siess M, Seybold G. Untersuchungen über die Wirkung von *Pulsatilla pratensis, Cimicifuga racemosa* und *Aristolochia clematitis* auf den Östrus infantiler und kastrierter weisser Mäuse. *Arzneimittel-Forschung,* 1960, 10:514–520.
39. Jarry H et al. Organ-specific effects of *Cimicifuga racemosa* (CR) in brain and uterus. In: *Proceedings of the Twenty-third International LOF-Symposium of Phyto-estrogens*. Ghent, 1999.
40. Benoit PS et al. Biological and phytochemical evaluation of plants. XIV. Anti-inflammatory evaluation of 163 species of plants. *Lloydia,* 1976, 39:160–171.
41. Liske E, Wüstenberg P. Efficacy and safety of phytomedicines with particular reference to *Cimicifuga racemosa*. *Journal of the Medical Association of Thailand,* 1998, 81 (Suppl. 1):S108.
42. Liske E, Wüstenberg P. Therapy of climacteric complaints with *Cimicifuga racemosa*: herbal medicine with clinically proven evidence [Abstract]. *Menopause,* 1998, 5:250.
43. Lieberman S. A review of the effectiveness of *Cimicifuga racemosa* (black cohosh) for the symptoms of menopause. *Journal of Women's Health,* 1998, 7:525–529.
44. Görlich N. Behandlung ovarieller Störungen in der Allgemeinpraxis. *Ärztliche Praxis,* 1962, 14:1742–1743.
45. Heizer H. Kritisches zur *Cimicifuga*-Therapie bei hormonalen Störungen der Frau. *Medizinische Klinik,* 1960, 55:232–233.
46. Schotten EW. Erfahrungen mit dem *Cimicifuga*-Präparat Remifemin. *Der Landarzt,* 1958, 11:353–354.
47. Starfinger W. Therapie mit östrogenwirksamen Pflanzenextrakten. *Medizin Heute,* 1960, 9:173–174.
48. Stiehler K. Über die Anwendung eines standardisierten *Cimicifuga*-Auszuges in der Gynäkologie. *Ärztliche Praxis,* 1959, 26:916–917.
49. Fukunishi K et al. Teratology study of hochu-ekki-to in rats. *Pharmacometrics,* 1997, 53:293–297.
50. Sakaguchi Y et al. Teratology study of otsuji-to in rats. *Pharmacometrics,* 1997, 53:287–292.