Bionorica®

Scientific Overview of Efficacy and Safety of Klimadynon® | Uno, Mensifem®, Menopret®, Menofem®

BNO 1055

Bionorica®

Short overview of the efficacy and tolerability Klimadynon® | Uno, Mensifem®

Hot flushes? Excessive sweating?

Klimadynon® | Uno, Mensifem®

- reduces hot flushes and sweating
- improves mental well-being
- works naturally

Klimadynon® (BNO 1055), also registered as **Klimadynon® Uno, Mensifem®, Menopret® and Menofem®**, utilises the dried extract from black cohosh (***Cimcifuga racemosa***), which, due to its phytopharmaceutical composition, works effectively against the different symptoms of menopause.

Klimadynon® and **Klimadynon® Uno** are available in tablet form from BIONORICA SE. It is effective in providing natural relief from the typical symptoms that women suffer from during menopause, such as hot flushes and sweating attacks.

Black Cohosh

Short overview of the efficacy and tolerability Klimadynon® | Uno, Mensifem®

Klimadynon's® efficacy has been well proven in GCP-compliant, randomised, placebo-controlled, double-blind studies. The indications for **Klimadynon®** are 'Menopausal and other perimenopausal disorders'.

Klimadynon® is a therapeutic agent recommended for use to combat certain symptoms of the menopausal and female climacteric state such as flushing, sleeplessness, headache and lack of concentration.

Klimadynon®, BNO 1055 – a pilot clinical study

In a pilot clinical study with 95 post-menopausal women aged between 40–60 years, patients were treated for 12 weeks with BNO 1055, conjugated estrogens or placebo. This prospective study conformed to Good Clinical Practice (GCP), was double-blind, placebo and conjugated estrogen-controlled and randomized. Menopause Rating Scores (MRS) were used to evaluate the climacteric complaints, using a 10-point standard for menopausal symptoms, including items such as hot flushes, palpitations, sleeplessness etc. Moreover, sweating episodes and sleeping behaviour were also evaluated based on the patient diaries. Analysis of the MRS showed that BNO 1055 was as effective as the conjugated estrogens in reducing climacteric complaints, when compared with the placebo group (***Fig. 1***).

As shown in ***Fig. 2***, where the MRS score was categorized and evaluated for three categories, viz. hot flushes, psyche and atrophy, BNO 1055 was significantly better than the placebo group in all cases. The symptoms affecting psyche (viz. despondency, nervousness, physical and mental fatigue and decrease in sexual desire) were ameliorated by **Klimadynon®**. Moreover, **Klimadynon®** was also more effective than the conjugated estrogen therapy in improving the atrophy symptoms like bladder problems, feeling of dryness in the vagina and joint pains (p = 0.0218). Both **Klimadynon®** and conjugated estrogen therapy were effective in reducing the symptoms associated with hot flushes when compared to the controls treated with placebo [1] (***Fig. 1 and 2***).

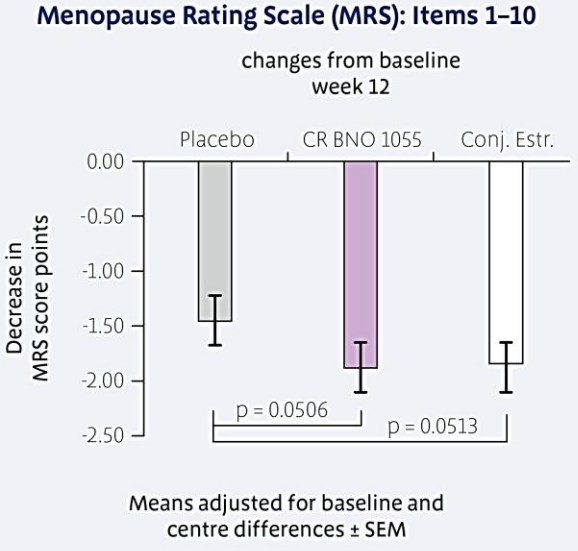


Fig. 1: Evaluation of MRS over the 12-week treatment period, where the placebo effect was outmatched by Klimadynon® and conjugated estrogen treatment (daily dose; corresponding to 40 mg herbal drug). These effects approached significance.

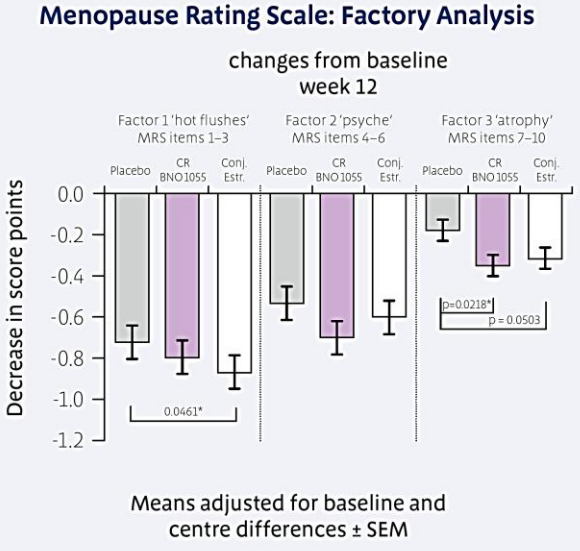


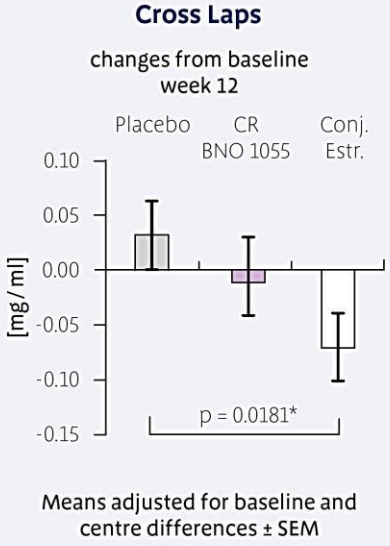
Fig. 2: For a better evaluation of MRS, the 10 items were combined into three factors. Factor 1 'hot flushes' was obviously improved by placebo and significantly improved under CE. With Klimadynon®, this effect was similar, but not statistically significant.
Factor 2 'psyche' was improved by placebo and further improved by CEs and Klimadynon®. Factor 3 'atrophy' was slightly influenced by placebo. A significant improvement was obtained under Klimadynon®, while CE approached significance.

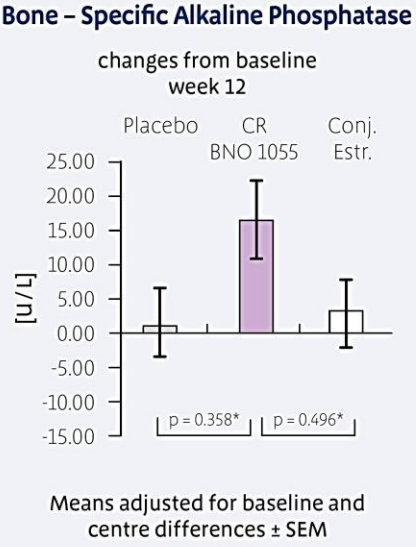
Klimadynon®, BNO 1055 – a pilot clinical study

BNO 1055 was equally effective to conjugated estrogens (CEs) in prevention of bone degradation, as was evident by the evaluation bone metabolism markers (collagen 1α1) in the serum. The value was increased in the placebo group, indicating degradation, whereas it remained unchanged after **Klimadynon®** and decreased after treatment with CEs[1] (*Fig. 3*).

In contrast, the value for bone-specific alkaline phosphatase (a metabolic marker for bone formation) was significantly increased after **Klimadynon®** treatment, while it remained unchanged in the placebo and CE groups[2] (*Fig. 4*).

Klimadynon® was also very successful in reducing the episodes of sweating per day in the clinical set up. The average frequency of episodes decreased after 4 weeks of treatment and were significantly lower compared to the placebo and CE treated groups[3] (*Fig. 5*).





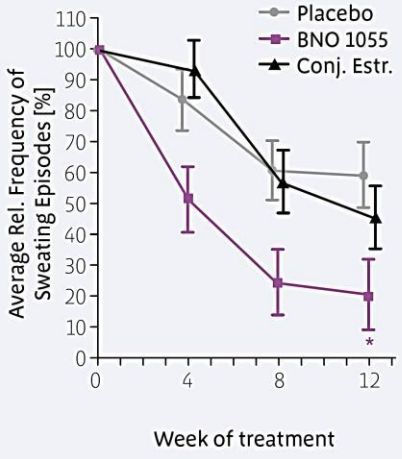


Fig. 3: Serum levels of CrossLaps (a marker for bone degradation) were significantly increased in the placebo group and were reduced by CE, while Klimadynon® showed no effect. The increased value represents a greater osteoclast cell activity which is responsible for bone degradation (Basle et al., 1988; Wuttke et al., 2003).

Fig. 4: Serum levels of bone-specific alkaline phosphatase were significantly increased after 12 weeks of treatment with Klimadynon®, an effect not seen under CE.

Fig. 5: Klimadynon® reduced the average relative frequency of sweating per day. The effects were clearly different from the 4th of week of treatment and attained significance over the placebo and CE group 12 weeks after the start of treatment.

Klimadynon®, BNO 1055 – Tolerability and Safety

Climacteric complaints, especially vasomotor symptoms (hot flushes, sweating) and vaginal dryness are treated with hormone therapy (Deutsche Gesellschaft für Gynäkologie and Geburtshilfe e. V. Hormontherapie in der Peri- and Postmenopause (HT). Interdisziplinäre S3-Leitlinie. Stand, 2009[4,5]). Comprehensive clinical studies in the 1990s and early 2000 (Women's Health Initiative Study (WHI) and Women's International Study of Long Duration Estrogen after Menopause (WISDOM), and Million Woman Initiative) have demonstrated, however, that women who were treated with hormone therapy for climacteric complaints for several years had a significantly increased risk of breast cancer, cardiovascular events, pulmonary embolism, and dementia when compared with to placebo[6,7].

In a systematic review[8], BNO 1055 was found to be a safe product based on various black cohosh products and publications that were evaluated.

The safety of **Klimadynon®** has been validated in 4 different clinical trials. Most notably, two separate clinical trials were performed to assess the tolerability of **Klimadynon®** in menopausal women. Study 1 was an open-label, non-comparative, prospective, multi-centre and multi-nation study, conducted in accordance with the GCP guidelines[9]. Study 2 was a longitudinal study carried out for 12 months with a further 12-month follow up[10].

STUDY 1: Proof of endometrial and general safety of BNO 1055
Number of subjects: 400
Groups: Placebo, open-label, multinational, multi-centre trial Klimadynon® (daily dose corresponding to 40 mg herb)
Good overall tolerability
No endometrial hyperplasia was observed
Endometrial thickness was not increased, as shown by endovaginal ultrasonography
The number and intensity of hot flushes were markedly decreased

STUDY 2: Effect on total hepatic perfusion and liver functions
Number of subjects: 87 (12-month follow up)
Groups: Healthy post-menopausal women
40 mg dry extract (BNO 1055) administered daily
Hepatic blood flow assessed by Doppler ultrasound
Prothrombin time, serum albumin, bilirubin, alkaline phosphatase, γ-glutamyltransferase and aspartate aminotransferase were evaluated
No evident significant changes were found in the total hepatic blood flow or liver functions

Conclusion

Klimadynon® did not have any adverse effects on vascular function, endometrial or hepatic perfusion and liver functions.

Systematic Evaluation of Clinical Studies

The clinical studies conducted on ***Cimicifuga racemosa*** were systematically reviewed by Borelli and Ernst[11]. In this study, black cohosh or its preparations were systematically evaluated for their efficacy in the treatment of menopausal symptoms. Only randomized controlled and double-blind studies, with women having at least one intact ovary, were selected for evaluation.

Furthermore, only mono-preparations containing black cohosh were selected. Articles were scored on an internationally accepted 5-point standard scaling system (Jadad scoring). A summary for the top-rated studies is given in the table below. This shows that the studies conducted on BNO 1055 received a complete Jadad score of 5 and were rated at the top.

Reference	Product	Main result	Jadad Score
Wuttke, 2003 and 2006[1,2]	CR BNO1055 (Klimadynon®)	Active treatment was better than placebo	5
Stoll, 1987[13]	Two tablets of 8 mg extract per day	*C. racemosa* improved all parameters compared to placebo	3
Osmers, 2005[14]	Isopropanolic Cohosh Extract	Women in early menopause experienced benefits	5
Frei-Kleiner, 2005[15]	Dried extract	No intergroup difference	4
Newton 2005 and 2006[16,17]	Multibotanical preparation along with Soy	Only significant difference in night sweats	5
Bai (2006 and 2007)[18]	Remifemin	Significant non-inferiority of black cohosh	4

Table: Excerpt from the results of a systematic evaluation of studies into Cimicifuga racemosa preparations (Borreli and Ernst, 2008)[12]

BNO 1055 – Pharmacological Evidence

BNO 1055 – preclinical findings: phyto-estrogens vs black cohosh

The secret behind the efficacy of Klimadynon® is the herbal drug black cohosh (*Cimcifuga racemosa*). Black cohosh is a plant that is very well known for its ability to act against the typical complications and symptoms associated with menopause.

Preclinical findings suggest that the efficacy of black cohosh extract BNO 1055 is a result of substances with dopaminergic or serotonergic activity. In contrast, a direct interaction of BNO 1055 with ERα or ERβ could not be identified (*Fig. 6*)[19]. BNO 1055 had no stimulatory effect on the mammary or endometrial tissue.

Pulsed release of luteinizing hormone (LH) in larger quantities occurs due to over-activation of hypothalamic GnRH. The neurotransmitters driving the GnRH pulse are spilled over to other hypothalamic neurons, which thereby affect the body temperature and cardiovascular activity. This pulsatile effect can be determined by withdrawing blood at regular intervals after the administration of test compounds. Estradiol (3.5 µg per animal per day) led to a reduction in the amplitude.

The effect of BNO 1055 and genistein (a phyto-estrogenic soy isoflavone) was evaluated in a controlled study in ovariectomized rats. While an acute i. v. injection of 3.5 mg genistein had no significant effect in reducing serum LH levels, the i. v. injection of 62.5 mg of **Klimadynon®** significantly ($p < 0.05$) suppressed LH levels (*Fig. 7*)[3].

Therefore, it appears that **Klimadynon®** does help in reducing hot flushes and tachycardia via modulation of GnRH pulse from the hypothalamus.

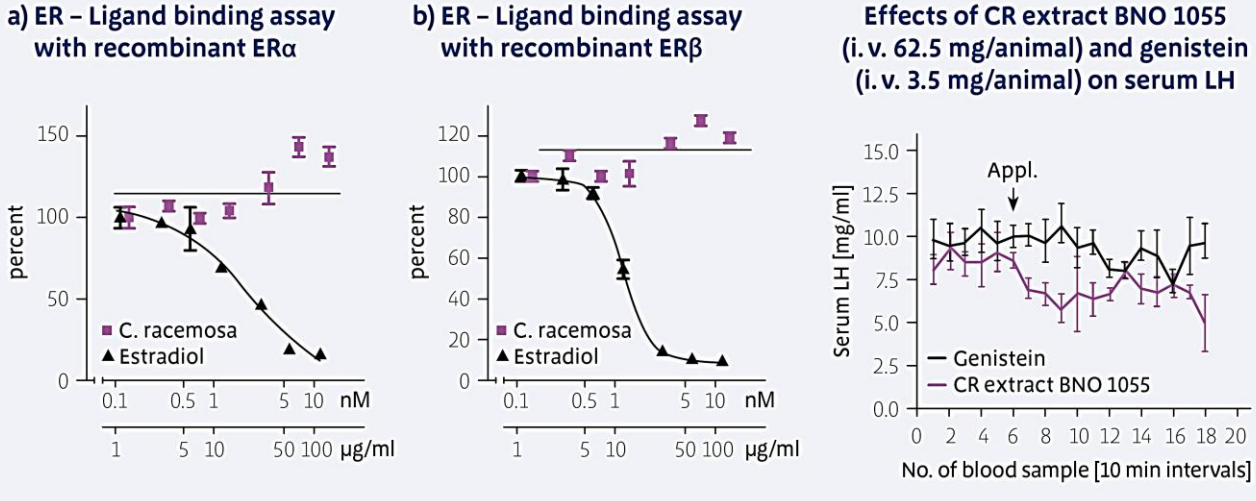


Fig. 6: Displacement curve of BNO estradiol and BNO 1055 from recombinant estrogen receptors (ER). In ligand binding assay with ERα (a) and ERβ (b) an increasing amount of estradiol displaced the radiolabelled estradiol increasingly from both receptor preparations. Such activity was not seen with an increasing amount of BNO 1055. This indicates that no substance in BNO 1055 competes with the radio-labelled estradiol for both receptor subtypes.

Fig. 7: Evaluation of the effect of BNO 1055 on serum LH level and its comparison to Genistein

Klimadynon® / Mensifem® – Not a Phyto-estrogen

Study and monographs

Studies have validated that **Klimadynon®** does not contain any of the 'classical phyto-estrogens'. No estrogen agonistic effects were found for **Klimadynon®**. The aqueous ethanolic extract of black cohosh (**Klimadynon®**) did not bind to the recombinant ERα and ERβ protein (***Fig. 6***)[19].

Scientific monographs published on black cohosh further validate the efficacy of the standardized preparation as an accepted alternative to hormone therapy (***Fig. 8***)[19].

Moreover, although having no estrogenic effects **Klimadynon®** was partially helpful in recovery of bone mineral density in ovx rats (***Fig. 9***).

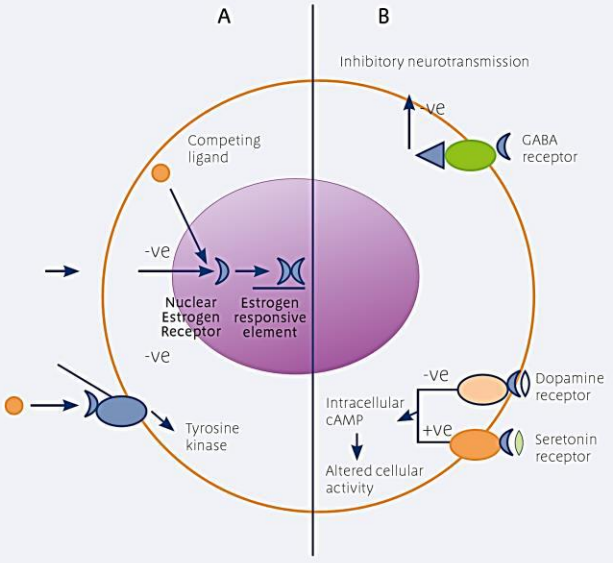


Fig. 8: Mechanistic overview of the action of black cohosh on two distinct putative pathways. On the left hand side of the figure, estrogen receptor mediated effects depend on competing residual endogenous estrogen. In contrast to phyto-estrogens, so far, only competitive inhibitory effects have been observed.

Effects of Klimadynon® (BNO 1005), Estradiol and Soy (administered orally for 12 weeks) on trabecular bone mineral density in the metaphysis of the tibia

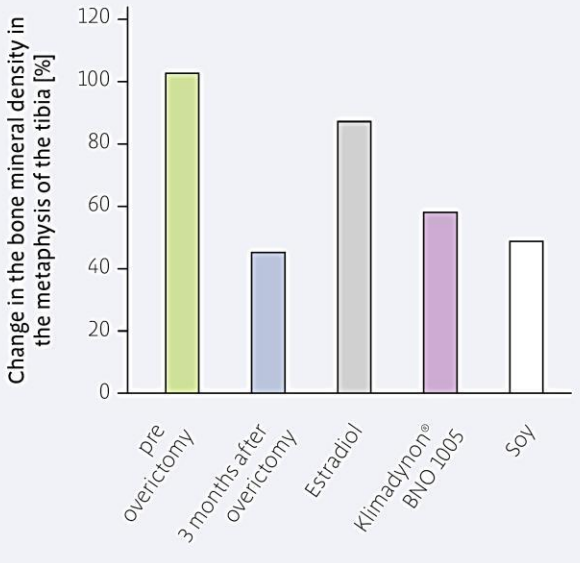


Fig. 9: Bone Marrow Density of the metaphysis of tibia bone. Note that >50% of BMD is lost in untreated ovx rats in comparison to E2-treated animals. CR extract BNO 1055 treatment had a partial but significant bone-sparing effect, which was not seen in the soy-fed animals (*P<0.05 vs. pre-ovx; #P<0.05 vs. 3 months after ovx)

Breast Safety

Three clinical trials demonstrated the low incidence of adverse reactions to black cohosh extracts, especially with reference to breast and endometrial safety.[3,9,21] In a clinical setting, black cohosh extract did not influence the recurrence or spreading of cancer when concomitantly administered with Tamoxifen. ***In vitro*** data showed non-proliferative effects of black cohosh extract and, on the other hand, confirmed the apoptotic effects of black cohosh in mammary carcinoma cells. In the study conducted by Raus et al., 138 mammograms were evaluated according to the standard BI-RADS classifications and there was no increase in breast density detected except in one woman, where a 0.72 % increase was observed. This was subsequently determined as not attributable to the BNO 1055 treatment.[9]

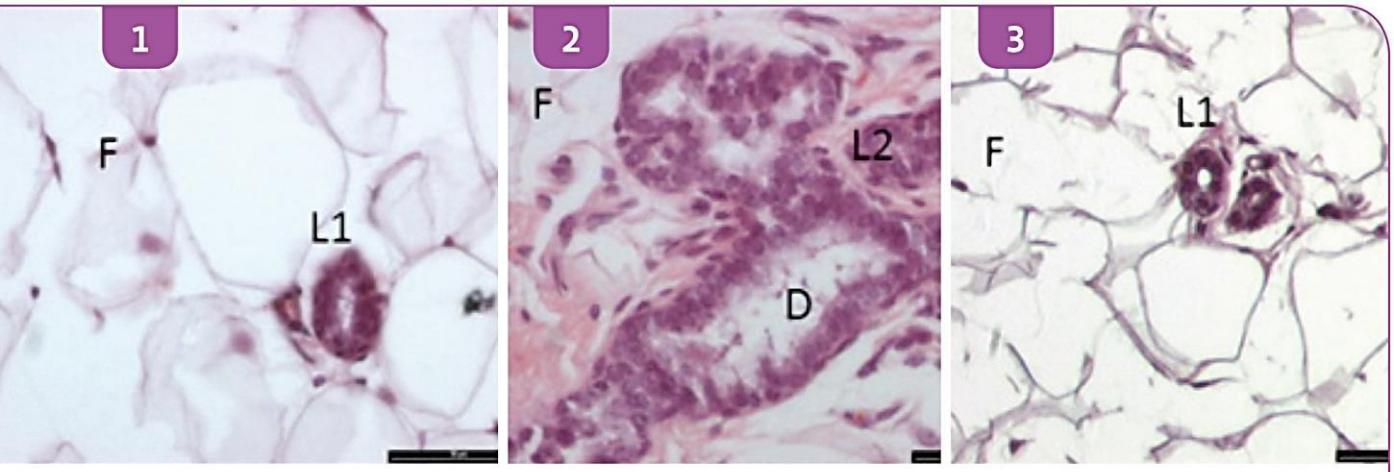


Fig. 10: Effects of estradiol (2) and CR BNO 1055 (3) in the mammary gland. Histological preparations of a mammary gland of (1) an ovariectomized (ovx) control rat, (2) of an ovx rat treated orally for 3 months with estradiol (0.05 mg/day) or (3) with CR BNO 1055 (30 mg/day). The relatively higher number of lobuli and ducti in the animal treated with estradiol in comparison to the negative control and the animal treated with CR BNO 1055 indicate that the black cohosh extract did not contain estrogenic compounds.

Endometrial Safety

Furthermore, in another open-label, multinational, multicentre study, endometrial safety was assessed based on endometrial biopsy samples and the tolerability and efficacy of the special ***Cimicifuga racemosa*** extract (CR BNO 1055).

Four hundred postmenopausal women with symptoms related to estrogen deficiency were treated for 52 weeks to determine the probability of endometrial hyperplasia and more serious adverse endometrial outcomes.

In conclusion of this study, no case of hyperplasia or more serious adverse endometrial outcome occurred (point estimate: 0.0; upper limit of 95% CI: 0.011). No increase was found in endometrial thickness, which was measured by endovaginal ultrasonography. The number and intensity of hot flushes were markedly decreased. The dropout rate was less than 10%. The overall tolerability was good. The final assessment of the study was that an improved benefit: risk ratio professes for BNO 1055 as a safe alternative for treatment of climacteric complaints.[3,9]

Vaginal Cytology

In a number of studies conducted on conjugated estrogens used as hormone therapy for PMS, there is evidence available that the CEs influence the vaginal cytology, increase the number of superficial cells compared to placebo and thus reduce vaginal dryness and itching. There was also an increase in the number of superficial cells reaching significance in the case of BNO 1055 administration, while the number of such cells was always lower in the placebo group.

Klimadynon® – *Cimicifuga racemosa* and its Background

Cimicifuga racemosa is a perennial plant of the ***Ranunculaceae*** (buttercup family). It is native to the Eastern US and Canada, from where all commercial stocks are normally derived. Indian tribes used the roots / rhizomes of this plant for medicinal use.

Based on a continuous discussion about the possible estrogenic activity of ***Cimicifuga racemosa***, a commission was set up by the European Medical Association and HMPC evaluations were tabled. The report mentioned that 'the recently analysed data do not support a direct estrogenic effect'. Due to the problems caused by Hormone Replacement Therapy (HRT) with chemical entities, products containing preparations of ***Cimicifuga racemosa*** are receiving ever more interest. Women with menopausal complaints, especially women undergoing breast cancer therapy, are also looking for alternatives to HRT, which is contraindicated in these patients. Chemically, an extract of the root and rhizome is known to contain at least three major natural product groups: cycloartenal-type triterpenes, phenolics and flavonoids (Al-Amier et al. 2005). Herbal preparations contain a complex mixture of triterpene glycosides; amongst them actein, cimifugosid and cimiracemosids. The total amount of triterpene glycosides is about 40 to 70 mg/g herbal substance (calculated as 27-deoxyactein).

Common names in Germany are: ***Cimicifuga***-Wurzelstock, Frauenwurzel, Nordamerikanische Schlangenwurzel, Wanzenkrautwurzel. In English, the plant is known as black cohosh; other common names are: black snakeroot, blackroot, rattleroot.

Cimicifuga racemosa

Klimadynon® – Aspects of Sustainability in the Procurement of Raw Materials

The quality of the raw material is decisive for the quality of the extract. Random collection of the plant material results in great fluctuations, e. g. in the pattern of constituents and microbial load, due to the large number of variables involved. Hence, it is better to draw the raw materials from known sources where cultivation and collection occur under controlled conditions.

Bionorica SE has been involved in a black cohosh domestication project for many years now. In close cooperation with the Humboldt University of Berlin, Bionorica carried out research on the optimisation of cultivation conditions. Furthermore, various origins were screened for quality in a breeding project. Selected genotypes were crossed with the aim of generating optimal varieties with an optimal spectrum of constituents and high-quality raw materials for the production of the finished drug.

The core objectives of the research project were:

- Optimisation of seedling production,
- Investigation of the changes in composition over the course of the year,
- Optimisation of the harvest time,
- Optimisation of postharvest handling (drying temperature and duration),
- Development of a method for DNA identification,
- Phytopathology

Growing seedlings and planting crops in Germany

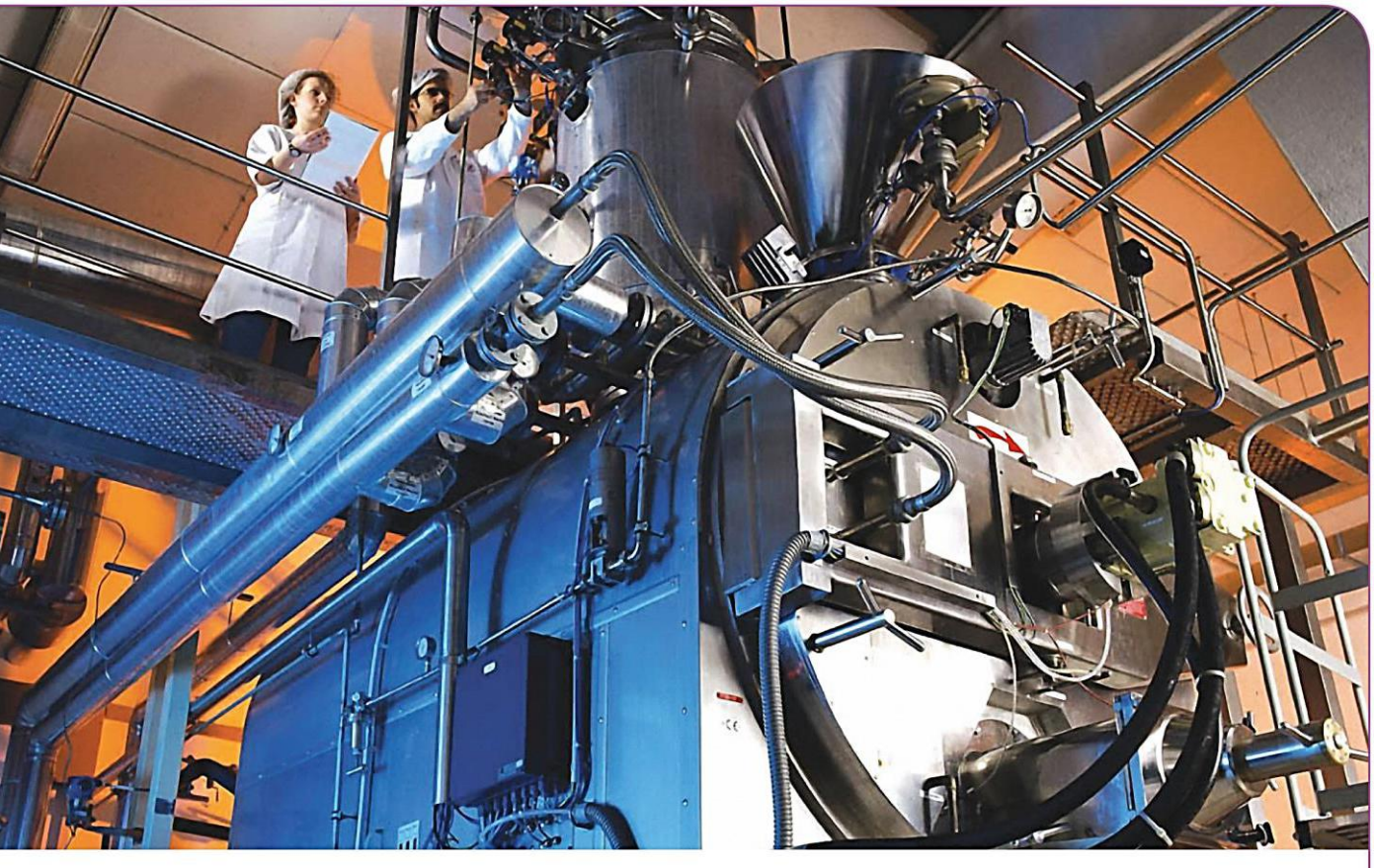
Growing period of 3–4 years prior to harvesting

Harvesting, washing and drying the root drug by the grower

Optimisation of this process was extremely time-consuming and expensive due to the slow growth. The findings were tested first in field trials. Nowadays, ***Cimicifuga*** is cultivated on commercial scale for Bionorica SE in Germany. Another important step on the way to a high-quality phytopharmaceutical product is the production method.

In the case of Bionorica's special ***Actaea racemosa*** extract BNO 1055, we have been using an internally developed and patented gentle method for years in the production of dry extracts under vacuum at low temperatures to protect the extremely delicate substances as well as possible and to retain them in the finished drug.

The quality of the extract is continuously monitored over the course of the production process – not only to adhere to the quality procedures required for authorisation, but also to satisfy our considerably higher in-house quality standards.

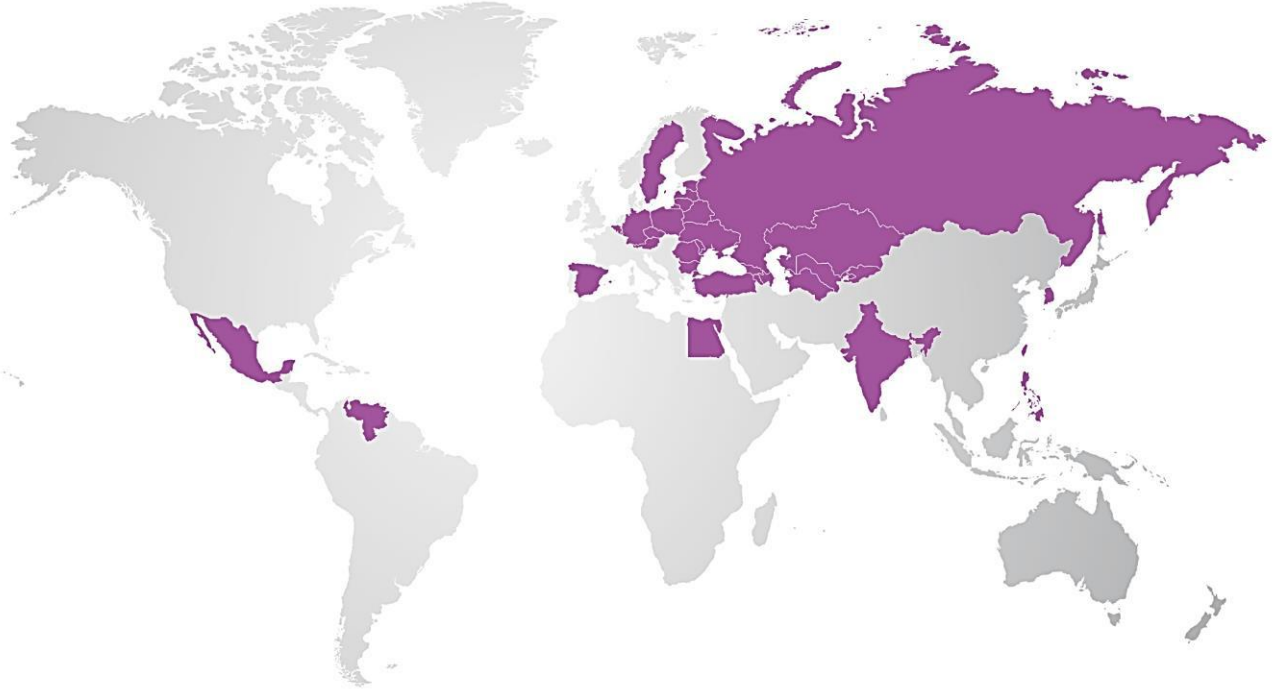


Patented extract drying process

Phytoneering – the formula for our success!

For over eighty years the name 'Bionorica' has stood for high quality and continuous improvement of herbal medicines. Treatment with products from Mother Nature, primarily medicinal herbs, has a centuries-old tradition and is a cornerstone of empirical medicine. We have used this tradition and placed it on a modern and rational, i. e. scientific and medically substantiated base. Over the last few decades we have worked hard to determine and document the potential effects of herbal ingredients using state-of-the-art methods. Today, Bionorica is one of the world's leading companies for research, development, production and marketing of phytopharmaceutical products.

Our identity, or unique selling proposition, lies in the phytoneering principle. Phytoneering stands for unlocking the great medicinal potential of plants (phyto-) through leading-edge research and innovative technologies (engineering) to produce effective and safe herbal medicines. A good example of this is the **Klimadynon®** brand: With **Klimadynon®** and **Klimadynon® Uno**, we offer you two strong black cohosh preparations on the German market. We are convinced that this reflects the satisfaction of physicians, chemists and users alike – and not only in Germany. Available in 32 countries around the world, the **Klimadynon®** brand has become a global success story.



References:

1. **Wuttke, W., D. Seidlova-Wuttke, and C. Gorkow,**
   The Cimicifuga preparation BNO 1055 vs. conjugated ostrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers.
   Maturitas, 2003. 44 Suppl 1: p. S67–77.

2. **Wuttke, W., C. Gorkow, and D. Seidlova-Wuttke,**
   Effects of black cohosh (Cimicifuga racemosa) on bone turnover, vaginal mucosa, and various blood parameters in postmenopausal women: a double-blind, placebo-controlled, and conjugated estrogens-controlled study.
   Menopause, 2006. 13(2): p. 185–196.

3. **Wuttke, W., K. Raus, and C. Gorkow,**
   Therapie von Zyklusstörungen mit Vitex agnus-castus. Zeitschrift für Phytotherapie 1994, 15,
   Maturitas, 2006. 55 (Supplement 1).

   Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e. V. Hormontherapie in der Peri- und Postmenopause (HT). Interdisziplinäre S3-Leitlinie. Stand, 2009.

4. **Schwabe, U. and D. Paffrath,**
   Arzneiverordnungs- Report 2008.
   2008, Heidelberg, Germany: Springer.

5. **Scheidt-Nave, C. and M. Dören,** eds.
   'Editorial' in Hormonetherapie bei (post-) menopausalen Frauen in Deutschland 2007. Studienergebnisse zu Nutzen, Risiken und Versorgungsrealität, Robert Koch-Institut.
   Vol. 2008. 2008: Berlin, German.

6. **Anderson, G.I., M. Limacher, and A.R. Assaf,**
   Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial.
   Journal of American Medical Association, 2004. 291(4): p. 1701–1712.

7. **Beer, A.M. and A. Neff,**
   Differentiated Evaluation of Extract-Specific Evidence on Cimicifuga racemosa's Efficacy and Safety for Climacteric Complaints.
   Evid Based Complement Alternat Med, 2013. 2013: p. 860602.

8. **Raus, K., et al.,**
   First-time proof of endometrial safety of the special black cohosh extract (Actaea or Cimicifuga racemosa extract) CR BNO 1055.
   Menopause, 2006. 13(4): p. 678–91.

9. **Nasr, A. and H. Nafeh,**
   Influence of black cohosh (Cimicifuga racemosa) use by postmenopausal women on total hepatic perfusion and liver functions.
   Fertil Steril, 2009. 92(5): p. 1780–2.

10. **Borrelli, F., A.A. Izzo, and E. Ernst,**
    Pharmacological effects of Cimicifuga racemosa.
    Life Sci, 2003. 73(10): p. 1215–29.

11. **Borrelli, F. and E. Ernst,**
    Black cohosh (Cimicifuga racemosa) for menopausal symptoms: a systematic review of its efficacy.
    Pharmacol Res, 2008. 58(1): p. 8–14.

12. **Stoll, W.,**
Phytopharmacon influences atrophic vaginal epithelium: double-blind study – Cimicifuga vs. estrogenic substances.
Therapeuticum, 1987. 1(23): p. 31.

13. **Osmers, R., et al.,**
Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms.
Obstetrics Gynaecology, 2005. 105(1074–1083).

14. **Frei-Kleiner, S., et al.,**
Cimicifuga racemosa dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial.
Maturitas, 2005. 51(4): p. 397–404.

15. **Newton, K.M., et al.,**
The Herbal Alternatives for Menopause (HALT) Study: background and study design.
Maturitas, 2005. 52(2): p. 134–46.

16. **Newton, K.M., et al.,**
Reprint of The Herbal Alternatives for Menopause (HALT) Study: background and study design.
Maturitas, 2008. 61(1–2): p. 181–93.

17. **Bai, W., et al.,**
Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: a randomized, double blind, parallel-controlled study versus tibolone.
Maturitas, 2007. 58(1): p. 31–41.

18. **Wuttke, W., et al.,**
The non-estrogenic alternative for the treatment of climacteric complaints: Black cohosh (Cimicifuga or Actaea racemosa).
J Steroid Biochem Mol Biol, 2014. 139: p. 302–10.

19. **Seidlova-Wuttke, D., et al.,**
Pharmacology of Cimicifuga racemosa extract BNO 1055 in rats: bone, fat and uterus.
Maturitas, 2003. 44 Suppl 1: p. S39–50.

20. **Winterhoff, H., et al.,**
[Pharmacologic and clinical studies using Cimicifuga racemosa in climacteric complaints].
Wien Med Wochenschr, 2002. 152(15–16): p. 360–3.

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