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List of references supporting the assessment of *Cimicifuga racemosa* (L.) Nutt., rhizoma

Draft

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AACE. Menopause Guidelines. *Endocr Pract* 2011, 17 (Suppl 6)

Adnan MM, Khan M, Hashmi S, Hamza M, Abdul Mujeeb S, Amer S. Black cohosh and liver toxicity: Is there a relationship? *Case Rep Gastrointest Med* 2014, doi 10.1155/2014/860614

Amato P, Christophe S, Mellon PL. Estrogenic activity of herbs commonly used as remedies for menopausal symptoms. *Menopause* 2002, 9(2): 145-150

Amsterdam JD, Yao Y, Mao JJ, Soeller I, Rockwell K, Shults J. Randomized, double-blind, placebo-controlled trial of *Cimicifuga racemosa* (black cohosh) in women with anxiety disorder due to menopause. *J Clin Psychopharmacol* 2009, 29(5):478-83

Antoine C, Liebens F, Carly B, Pastijn A, Rozenberg S. Safety of alternative treatments for menopausal symptoms after breast cancer: a qualitative systemic review. *Climacteric* 2007, 10: 23-26 Available at: <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133343.pdf>

Bai W, Henneicke-von Zepelin HH, Wang S, Zheng S, Liu J, Zhang Z, *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: 31-41

Bartsch HH, Fischer J, *et al.* AWB mit Remifemin bei Mamma-Ca-Patientinnen mit klimakterischen Beschwerden unter Tamoxifen: Integrierter medizinischer und biometrischer Bericht, Schaper & Brümmer. Data published in Thesis: Juliane Fischer: *Cimicifuga racemosa* Extrakt (Remifemin®) bei Mamma-Ca-Patientinnen mit klimakterischen Beschwerden unter hormontherapeutischer Behandlung mit Tamoxifen – eine Anwendungsbeobachtung. Albert-Ludwigs-Universität Freiburg i.Br. 2006



- Bebenek M, Kemmler W, von Stengel S, Engelke K, Kalender WA. Effect of exercise and *Cimicifuga racemosa* (CR BNO 1055) on bone mineral density, 10-year coronary heart disease risk, and menopausal complaints: the randomized controlled Training and *Cimicifuga racemosa* Erlangen (TRACE) study. *Menopause* 2010, 17(4):791-800
- Becher H, Henneicke-von Zepelin HH, Schröder-Bernhardi D, Stammwitz U. Pharmakoepidemiologische Kohortenstudie zur Anwendung von Remifemin® / Remifemin®Plus bei Patientinnen mit Mammakarzinom einschließlich Hormonrezeptor positiver Tumoren. *J Menopause* 2/2005 Abstract Kongress der DGM
- Beer AM, Neff A. Differentiated evaluation of extract-specific evidence on *Cimicifuga racemosa*'s efficacy and safety for climacteric complaints. *Evid Based Complement Alternat Med* 2013, doi 10.1155/2013/860602
- Beer AM, Osmers R, Schnitker J, Bai W, Mueck AO, Meden H. Efficacy of black cohosh (*Cimicifuga racemosa*) medicines for treatment of menopausal symptoms - comments on major statements of the Cochrane Collaboration report 2012 "black cohosh (*Cimicifuga* spp.) for menopausal symptoms (review)". *Gynecol Endocrinol.* 2013, 29: 1022-1025.
- Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs-II. An original model for validation of drug causality assessment methods: Case reports with positive rechallenge. *J Clin Epidemiol* 1993, 46(11): 1331-1336
- Blaschek W, Ebel S, Hackenthal E, Holzgrabe U, Keller K, Reichling J, Schulz V, editors. *Hagers Enzyklopädie der Drogen und Arzneistoffe*. 6., neu bearbeitete und ergänzte Auflage, Band 4, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 2007, 644-661
- Boekhout AH, Beijnen JH, Schellens JHM. Symptoms and treatment in cancer therapy-induced early menopause. *Oncologist* 2006, 11: 641-654
- Bordeleau L, Pritchard K, Goodwin P, Loprinzi C. Therapeutic options for the management of hot flashes in breast cancer survivors: an evidence-based review. *CLIN THER* 2007, 29(2): 230-241
- Borrelli F, Ernst E. Black cohosh (*Cimicifuga racemosa*) for menopausal symptoms: a systematic review of its efficacy. *Pharmacol Res* 2008, 58(1):8-14
- Brasky TM, Lampe JW, Potter JD, Patterson RE, White E. Specialty supplements and breast cancer risk in the VITamins And Lifestyle (VITAL) Cohort. *Cancer Epidemiol Biomarkers Prev* 2010, 19(7):1696-1708
- Brattstroem A. Dosisabhängige Überlegenheit eines neu entwickelten *Cimicifuga* Extraktes (Ze 450). Eine doppelblinde, randomisierte und Placebo kontrollierte klinische Studie bei menopausalen Beschwerden. *Kongressband Phytopharmaka Phytotherapie* 2005, 6
- Briese V, Stammwitz U, Friede M, Henneicke-von Zepelin HH. Black cohosh with or without St. John's wort for symptom-specific climacteric treatment – results of a large-scale, controlled, observational study. *Maturitas* 2007, 57: 405-414
- Bruno D, Feeney KJ. Management of postmenopausal symptoms in breast cancer survivors. *Semin Oncol* 2006, 33: 696-707
- Burdette JE, Liu J, Chen SN, Fabricant DS, Piersen CE, et al. Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor. *J Agric Food Chem* 2003, 51: 5661-5670

- Campos LB, Gilglioni EH, Garcia RF, Brito MdN, Natali MRM, Ishii-Iwamoto EL, *et al.* Cimicifuga racemosa impairs fatty acid β -oxidation and induces oxidative stress in livers of ovariectomized rats with renovascular hypertension. *Free Radic Biol Med* 2012, 53: 680-689
- Carlisle A, Jessup JV. Effect of black cohosh on biochemical markers of bone remodeling in postmenopausal women. Dissertation, University of Florida, USA, 2008
- Carpenter J. State of the science: hot flashes and cancer. Part 2: Management and future directions. *Oncol Nurs Forum* 2005, 32(5): 969-978
- Chan BY, Lau KS, Kennelly EJ, Kronenberg F, Kung AWC. Ethanolic extracts of *Actaea racemosa* (black cohosh) potentiates bone nodule formation in MC3T3-E1 preosteoblast cells. *Bone* 2008, 43: 567-73
- Chlebowski RT, Kim JA, Col NF. Estrogen deficiency symptom management in breast cancer survivors in the changing context of menopausal hormone therapy. *Semin Oncol* 2003, 30(6): 776-788
- Commission E (Germany), Monographie: Cimicifugae racemosae rhizoma (Cimicifugawurzelstock), BAnz Nr. 43, 02.03.1989
- Commission E (Germany), Monographie: Cimicifugae racemosae rhizoma (Cimicifugawurzelstock), Revision (not published), 14 December 1994
- Daiber W. Klimakterische Beschwerden: ohne Hormone zum Erfolg, *Ärztliche Praxis, Die Zeitung des Arztes in Klinik und Praxis*, Sonderdruck; XXXV 1983, 65: 1946-1947
- Danan G, Benichou C. Causality assessment of adverse reactions to drugs - I. A novel method based on the conclusions of international consensus meetings: Application to drug-induced liver injuries, *J Clin Epidemiol* 1993, 46(11): 1323-1330
- Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. *Int J Mol Sci* 2015, 17(1), doi 10.3390/ijms17010014
- Davis VL, Jayo MJ, Hardy ML, Ho A, Lee H, *et al.* Effects of black cohosh on mammary tumor development and progression in MMTV-neu transgenic mice. *Proceedings of the AACR* 2003, 44: Abstract 910
- Davis VL, Jayo MJ, Ho A, Kotlarczyk MP, Hardy ML, *et al.* Black cohosh increases metastatic mammary cancer in transgenic mice expressing c-erbB2. *Cancer Res* 2008, 68(20): 8377-8383
- Dixon-Shanies D, Shaikh N. Growth inhibition of human breast cancer cells by herbs and phytoestrogens. *ONCOL REP* 1999, 6: 1383-1387
- Drewe J, Bucher KA, Zahner C. A systematic review of non-hormonal treatments of vasomotor symptoms in climacteric and cancer patients. *SpringerPlus* 2015, 4:65, doi 10.1186/s40064-015-0808-y
- Drewe J, Zimmermann C, Zahner C. The effect of a Cimicifuga racemosa extracts Ze 450 in the treatment of climacteric complaints - an observational study. *Phytomed* 2013, 20(8-9):659-666.
- Einbond LS, Shimizu M, Nuntanakorn P, Seter C, Cheng R, *et al.* Actein and a fraction of black cohosh potentiate antiproliferative effects of chemotherapy agents on human breast cancer cells. *Planta Med* 2006, 72: 1200-1206
- Einbond LS, Su T, Friedman R, Wang X, Ramirez A, *et al.* The growth inhibitory effect of actein on human breast cancer cells is associated with activation of stress response pathways. *INT J CANCER* 2007a, 121(9): 2073-2083

Einbond LS, Su T, Wu HA, Friedman R, Wang X, *et al.* Gene expression analysis of the mechanisms whereby black cohosh inhibits human breast cancer cell growth. *Anticancer Res* 2007b, 27: 697-712

Einer-Jensen N, Zhao J, Andersen KP, Kristoffersen K. Cimicifuga and Melbrosia lack oestrogenic effects in mice and rats. *Maturitas* 1996, 25: 149-153

EMA, HMPC. Assessment of case reports connected to herbal medicinal products containing Cimicifugae racemosae rhizoma (Black cohosh, root), EMEA/HMPC/269258/2006 Rev. 1. London, 8 May 2007. Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_HMPC_assessment_report/2010/02/WC500074167.pdf

EMA, HMPC. Guideline on the assessment of clinical safety and efficacy in the preparation of European Union herbal monographs for the well-established and of European Union herbal monographs / entries to the European Union list for traditional herbal medicinal products / substances / preparations, EMEA/HMPC/104613/2005, London 7 September 2006. Available at:
http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500003644

EMA. Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women. EMEA/CHMP/021/97 Rev. 1, London 13 October 2005. Available at:
http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500003348

Enbom ET, Le MD, Oesterich L, Rutgers J, French SW. Mechanism of hepatotoxicity due to black cohosh (Cimicifuga racemosa): histological, immunohistochemical and electron microscopy analysis of two liver biopsies with clinical correlation. *Exp Mol Pathol* 2014, 96(3):279-283

ESCAP Monographs 2nd edition. Cimicifugae rhizoma – Black cohosh. European Scientific Cooperative on Phytotherapy, editor. Thieme, Stuttgart 2003, 79-91

Fischer J. Cimicifuga racemosa Extrakt (Remifemin) bei Mamma-Ca-Patientinnen mit klimakterischen Beschwerden unter hormontherapeutischer Behandlung mit Tamoxifen – eine Anwendungsbeobachtung. PhD Thesis, Albert Ludwig Universität Freiburg. 2006

Frei-Kleiner S, Schaffner W, Rahlfs VW, Bodmer C, Birkhäuser M. Cimicifuga racemosa dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial. *Maturitas* 2005, 51: 397-404

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

Freudenstein J, Dasenbrock C, Nisslein T. Lack of promotion of estrogen-dependent mammary gland tumors in vivo by an isopropanolic Cimicifuga racemosae extract. *Cancer Res* 2002, 62: 3448-3452

Freudenstein J. Addendum to the 6-month oral toxicity study: Calculation of the dosages and the corresponding safety factors in the 6-month oral toxicity study, IBR Project No.: 20-04-0913-90, 1991, 26 September 1997

Fritz H, Seely D, McGowan J, Skidmore B, Fernandes R, Kennedy DA, *et al.* Black cohosh and breast cancer: a systematic review. *Integr Cancer Ther.* 2014, 13(1): 12-29

Garita-Hernandez M, Calzado MA, Caballero FJ, Macho A, Munoz E, *et al.* The growth inhibitory activity of the cimicifuga racemosa extract ZE 450 is mediated through estrogen and progesterone receptors-independent pathways. *Planta Med* 2006, 72: 317-323

Geller SE, Shulman LP, van Breemen RB, Banuvar S, Zhou Y, *et al.* Safety and efficacy of black cohosh and red clover for the management of vasomotor symptoms: a randomized controlled trial. *Menopause* 2009, 16(6): 1156-1166

Georgiev DB, Jordanova E. Phytoestrogens – the alternative approach. *Maturitas* 1997, 27: 213 (abstract P309)

Gurley BJ, Hubbard MA, Williams DK, Thaden J, Tong Y, *et al.* Assessing the clinical significance of botanical supplementation on human cytochrome P450 3A activity: comparison of a Milk Thistle and Black Cohosh product to Rifampin and Clarithromycin. *J Clin Pharm* 2006a, 46: 201-213

Gurley BJ, Barone GW, Williams DK, Carrier J, Breen P, *et al.* Effect of milk thistle (*Silybum marianum*) and black cohosh (*Cimicifuga racemosa*) supplementation on digoxin pharmacokinetics in humans. *Drug Metabol Dispos* 2006b, 34(1): 69-74

Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, *et al.* In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. *Clin Pharm Ther* 2005, 77(5): 415-426

Guzman G, Kallwitz ER, Wojewoda C, Chennuri R, Berkes J, *et al.* Liver injury with features mimicking autoimmune hepatitis following the use of black cohosh. *Case Reports in Medicine* 2009, Article ID 918156

Hall E, Frey BN, Soares CN. Non-hormonal treatment strategies for vasomotor symptoms: a critical review. *Drugs* 2011, 71(3): 287-304

Heinemann LHJ, Potthoff P, Schneider HPG. Health and quality of life outcomes, review international versions of the menopause rating scale (MRS) 2003. Available at: <http://www.hqlo.com/content/1/1/28>

Heinemann K, Ruebig A, Potthoff P, Schneider HPG, Heinemann LAJ, *et al.* The Menopause Rating Scale (MRS) scale: A methodological review. *Health and Quality of Life Outcomes* 2004, 2: 45

Heinemann LAJ, DoMinh T, Strelow F, Gerbsch S, Schnitker J, *et al.* The Menopause Rating Scale (MRS) as outcome measure for hormone treatment? A validation study. *Health and Quality of Life Outcomes* 2004b, 2: 67

Henneicke-von Zepelin HH, Meden H, Kostev K, Schröder-Bernhardt D, Stammwitz U, *et al.* Isopropanolic black cohosh extract and recurrence-free survival after breast cancer. *J Clin Pharmacol Ther* 2007, 45(3): 143-154

Hickey M, Saunders CM, Stuckey BGA. Management of menopausal symptoms in patients with breast cancer: an evidence-based approach. *Lancet Oncol* 2005, 6: 687-695

Hillmann E. Final report on the mutagenicity testing Salmonella/Microsome Test (Ames Test). Schaper & Brümmer unpublished study, Project No.: 95-92-1189-90, 1990

Hirschberg AL, Edlund M, Svane G, Azavedo E, Skoog L, von Schoultz B. An isopropanolic extract of black cohosh does not increase mammographic breast density or breast cell proliferation in postmenopausal women. *Menopause* 2007, 14: 89-96

Huang Y, Jiang B, Nuntanakorn P, Kennelly EJ, Shord S, Lawal TO, *et al.* Fukinolic acid derivatives and triterpene glycosides from black cohosh inhibit CYP isozymes, but are not cytotoxic to Hep-G2 cells in vitro. *Curr Drug Saf* 2010, 5(2):118-24.

Jacobson JS, Troxel AB, Evans J, Klaus L, Vahdat L, *et al.* Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *J CLIN ONCOL* 2001, 19(10): 2739-2745

Jarry H, Metten M, Spengler B, Christoffel V, Wuttke W. In vitro effects of the cimicifuga racemosa extract BNO 1055. *Maturitas* 2003, 44: 31-38

Jarry H, Harnischfeger G, Düker E. Untersuchungen zur endokrinen Wirksamkeit von Inhaltsstoffen aus Cimicifuga racemosa, 2. In vitro-Bindung von Inhaltsstoffen an Östrogenrezeptoren. *Planta Med* 1985a, 51(4): 316-319

Jarry H, Harnischfeger G. Untersuchungen zur endokrinen Wirksamkeit von Inhaltsstoffen aus Cimicifuga racemosa, 1. Einfluß auf die Serumspiegel von Hypophysenhormonen ovariectomierter Ratten. *Planta Med* 1985b, 51(1): 46-49

Kaiser WD, Martin R, Schellenberg R, Schrader E, Saller R. Cimicifuga-racemosa-Extrakt ZE 450 bei Wechseljahrsbeschwerden Praxisstudie. *Ars Medici* 2008, 17: 771-774

Kapur P, Wuttke W, Seidlova-Wuttke D. The Cimicifuga racemosa special extract BNO 1055 prevents hot flashes in ovariectomized rats. *Phytomed* 2010, 17(11): 890-4.

Kenemans P. Climacteric and postmenopause: definitions, terms and concepts. Available at: <http://www.womanlab.com/english/professionals/menopausalIssues1.htm>

King MT, Harnasch D. Mutagenicity study of Cimicifugawurzelstock-TE SteiCim 73 (100% native) in the Salmonella typhimurium/mammalian microsome reverse mutation assay (Ames-Test). Freiburger Labor für Mutagenitätsprüfung der King & Harnasch GmbH, Kirchzarten, unpublished study, project No. AM02102N, 2002.

Korn WD. 6-month oral toxicity study with "Remifemin-Granulate" in rats followed by an 8-week recovery period. Schaper & Brümmer, unpublished study, IBR Project No. 20-04-0913-90, 1991

Kretschmar G, Nisslein T, Zierau O, Vollmer G. No estrogen-like effects of an isopropanolic extract of rhizoma Cimicifugae racemosae on uterus and vena cava of rats after 17 day treatment. *Journal of Steroid Biochemistry & Molecular Biology* 2005, 97: 271-277

Kronenberg F, Warren M, Coletton M, Jin Z, McMahon DJ, Sauberli W. Effect of black cohosh extract on hot flashes and other menopausal symptoms. Poster presentation, 20th Annual Meeting, North American Menopause Society, San Diego, CA 2009

Kupperman HS, Blatt MHG, Wiesbader H, Filler W. Comparative clinical evaluation of estrogenic preparations by the menopausal and amenorrheal indices. *J Clin Endocrinol* 1953, 13: 688-703

Leach MJ, Moore V. Black cohosh (Cimicifuga spp.) for menopausal symptoms. *Cochrane Database Syst Rev*. 2012, 9: CD007244, doi 10.1002/14651858.CD007244.pub2

Lehmann-Willenbrock E, Riedel HH. Klinische und endokrinologische Untersuchungen zur Therapie ovarieller Ausfallserscheinungen nach Hysterektomie unter Belassung der Adnexe. *Zentbl Gynäkol* 1988, 110: 611-618

- Li J, Gödecke T, Chen S-N, Imai A, Lankin DC, Farnsworth NR, *et al.* In vitro metabolic interactions between black cohosh (*Cimicifuga racemosa*) and tamoxifen via inhibition of cytochromes P450 2D6 and 3A4. *Xenobiotica* 2011, 41:1021-30.
- Lim TY, Considine A, Quaglia A, Shawcross DL. Subacute liver failure secondary to black cohosh leading to liver transplantation. *BMJ Case Rep* 2013, doi 10.1136/bcr-2013-009325
- Liske E, Boblitz N, Henneicke-von Zepelin HH. Therapie klimakterischer Beschwerden mit *Cimicifuga racemosa* – Daten zur Wirkung und Wirksamkeit aus einer randomisierten kontrollierten Doppelblindstudie. In: Rietbrock, ed, *Phytopharmaka VI Forschung und klinische Anwendung*. Steinkopff, Darmstadt 2000, 247-257
- Liske E, Hänggi W, Henneicke-von Zepelin HH, Boblitz N, Wüstenberg P, *et al.* Physiological investigation of a unique extract of black cohosh (*cimicifugae racemosa rhizoma*): A 6-month clinical study demonstrates no systemic estrogenic effect. *Journal of Women's Health & Gender-Based Medicine* 2002, 11: 163-174
- Liske E, Boblitz N. Kooperation Phytopharmaka: *Cimicifuga racemosa* rhizome. Kooperation Phytopharmaka 1999, Aktualisiertes Wissenschaftliches Erkenntnismaterial 1999
- Liu ZP, Yu B, Huo JS, Lu CQ, Chen JS. Estrogenic effects of *Cimicifuga racemosa* (Black cohosh) in mice and on estrogen receptors in MCF-7 cells. *J Med Food* 2001, 4(3): 171-178
- Löhning A. Beitrag zur pharmakologischen Charakterisierung von Zubereitungen aus *Cimicifuga racemosa* Nutt., Ranunculaceae. Inaugural dissertation, conclusion. Westfälische Wilhelm-Universität Münster 1999
- Löhning A, Diel P, Verspohl EJ, Winterhoff H. In vitro studies on the estrogenic and dopaminergic activity of *Cimicifuga racemosa*. *N-S Arch Pharmacol* 1999a, 311: 359
- Löhning A, Verspohl EJ, Winterhoff H. Pharmacological studies on the dopaminergic activity of *Cimicifuga racemosa*. Workshop of the society for medicinal plant research (Gesellschaft für Arzneipflanzenforschung – GA) 1999b
- Löhning A, Verspohl EJ, Winterhoff H. Pharmacological studies on the central activity of *Cimicifuga racemosa* in mice. 46th Annual congress of the Society 1998, Abstract J10
- Lopatka L, Totzke U, Schmid A, Käufeler R. Die Traubensilberkerze in der Behandlung menopausaler Beschwerden - Ergebnisse einer Therapiebeobachtung mit Cimifemin® uno [Black cohosh in the treatment of menopausal complaints – results of an observational study with Cimifemin® uno]. *Journal für Menopause* 2007, 14(2): 16-21
- Lüde S, Török M, Dieterle S, Knapp AC, Kaeufeler R, *et al.* Hepatic effects of *Cimicifuga racemosa* extract in vivo and in vitro. *Cell Mol Life Sci* 2007, 64(21): 2848-2857
- Lüde S, Török M, Dieterle S, *et al.* Erratum to: Hepatic effects of *Cimicifuga racemosa* extract in vivo and in vitro. *Cell Mol Life Sci* 2010, 67: 2507
- Meyer S, Vogt T, Obermann EC, Landthaler M, Karrer S. Cutaneous pseudolymphoma induced by *Cimicifuga racemosa*. *Dermatology* 2007, 214: 94-96
- Mielnik J. Extracts of *Cimicifuga racemosa* in the treatment of neurovegetative symptoms in women in the perimenopausal period. *Maturitas* 1997, 27: 215

- Minciullo PL, Saija A, Patafi M, Marotta G, Ferlazzo B, *et al.* Muscle damage induced by black cohosh (*Cimicifuga racemosa*). *Phytomed* 2006, 13: 115-118
- Mohammad-Alizadeh-Charandabi S, Shahnazi M, Nahae J, Bayatipayan S. Efficacy of black cohosh (*Cimicifuga racemosa* L.) in treating early symptoms of menopause: a randomized clinical trial. *Chin Med* 2013, 8(1):20, doi 10.1186/1749-8546-8-20
- Mollá JMD, García-Sánchez Y, Romeu Sarri A, Pérez-López FR. *Cimicifuga racemosa* treatment and health related quality of life in post-menopausal Spanish women. *Gynecol Endocrinol* 2009, 25(1): 21-26
- Moyad M. Complementary/alternative therapies for reducing hot flashes in prostate cancer patients: reevaluating the existing indirect data from studies of breast cancer and postmenopausal women. *Urology* 2002, 59(4A): 20-33
- Munoz GH, Pluchino S. *Cimicifuga racemosa* for the treatment of hot flushes in women surviving breast cancer. *Maturitas* 2003, 44(1): 59-65
- Nappi R, Malavasi B, Brundu B, Facchinetti F. Efficacy of *Cimicifuga racemosa* on climacteric complaints: a randomized study versus low-dose transdermal estradiol. *GYNECOL ENDOCRINOL* 2005, 20(1): 30-35
- Nesselhut T, Liske E. Pharmacological measures in postmenopausal women with an isopropanolic aqueous extract of *Cimicifugae racemosa* rhizoma. *Menopause* 1999, 6(4): 8
- Nesselhut T, Schellhase C, Dietrich R, Kuhn W. Untersuchungen zur proliferativen Potenz von Phytopharmaka mit östrogenähnlicher Wirkung bei Mammakarzinomzellen, Abstract des Vortrages von Dr. Nesselhut 8.9.92, Kongreß der Deutschen Gesellschaft für Gynäkologie, Berlin, *Archives of Obstet Gynecol* 1993, 254: 817-818
- Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, *et al.* Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy or placebo. *Ann Intern Med* 2006, 145: 869-879
- Nisslein T, Freudenstein J. Concomitant administration of an isopropanolic extract of black cohosh and tamoxifen in the in vivo tumor model of implanted RUCA-I rat endometrial adenocarcinoma cells. *TOXICOL LETT* 2004, 150: 271-275
- Nisslein T, Freudenstein J. Effects of an isopropanolic extract of *Cimicifuga racemosa* on urinary crosslinks and other parameters of bone quality in an ovariectomized rat model of osteoporosis. *J BONE MINER METAB* 2003, 21: 370-376
- Obi N, Chang-Claude J, Berger J, Braendle W, Slinger T, *et al.* The use of herbal preparations to alleviate climacteric disorders and risk of postmenopausal breast cancer in a German case-control study. *Cancer Epidemiol Biomarkers Prev* 2009, 18: 2207-2213
- Öktem M, Eroglu D, Karahan HB, Taskintuna N, Kuscu E, *et al.* Black cohosh and Fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized trial. *ADV THER* 2007, 24(2): 448-461
- Osmer R, Friede M, Liske E, Schnitker J, Freudenstein J, *et al.* Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol* 2005, 105(5): 1074-1083
- Palacio C, Masri G, Mooradian AD. Black cohosh for the management of menopausal symptoms; A systematic review of clinical trials. *Drugs Aging* 2009, 26(1): 23-36

- Palacios S, Ferrer-Barriendos J, Parrilla JJ, Castelo-Branco C, Manubens M, *et al.* [Health-related quality of life in the Spanish women through and beyond menopause. Development and validation of the Cervantes Scale.] *Med Clin (Barc)* 2004, 122(6): 205-211
- Patel NM, Derkits RM. Possible increase in liver enzymes secondary to Atorvastatin and black cohosh administration. *J Pharm Pract* 2007, 20(4): 341-346
- Pethö A. Umstellung einer Hormonbehandlung auf ein pflanzliches Gynäkologikum möglich?, *Ärztliche Praxis - Zeitung des Arztes in Klinik und Praxis* 1987; Sonderdruck XXXIX. Jahrgang Nr. 47: 1551-1553
- Pockaj BA, Gallagher JG, Loprinzi CL, Stella PJ, Barton DL, *et al.* Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG Trial N01CC. *J Clin Oncol* 2006, 24(18): 2836-2841
- Pockaj BA, Loprinzi CL, Sloan JA, Novotny PJ, Barton DL, *et al.* Pilot evaluation of black cohosh for the treatment of hot flashes in women. *Cancer Invest* 2004, 22(4): 515-521
- Powell SL, Gödecke T, Nikolic D, Chen SN, Ahn S, *et al.* In vitro serotonergic activity of black cohosh and identification of Na-Methylserotonin as a potential active constituent. *Journal of Agricultural and Food Chem* 2008, 56: 11718-11726
- Qiu SX, Dan C, Ding LS, Peng S, Chen SN, Farnsworth NR, *et al.* A Triterpene Glycoside from Black Cohosh that Inhibits Osteoclastogenesis by Modulating RANKL and TNF α Signaling Pathways. *Chem Biol* 2007, 14(7): 860-869
- Raus K, Brucker C, Gorkow C, Wuttke W. First-time proof of endometrial safety of the special black cohosh extract (Actaea or Cimicifuga racemosa extract) CR BNO 1055. *Menopause* 2006, 13(4): 678-691
- Rebbeck TR, Troxel AB, Norman S, Bunin GR, DeMichele A, *et al.* A retrospective case-control study of the use of hormone-related supplements and association with breast cancer. *INT J CANCER* 2007, 120(7): 1523-1528
- Reed SD, Newton KM, LaCrois AZ, Grothaus LC, Grieco V, *et al.* Vaginal, endometrial, and reproductive hormone findings: randomized, placebo-controlled trial of black cohosh, multibotanical herbs, and dietary soy for vasomotor symptoms: the Herbal Alternatives for Menopause (HALT) Study. *Menopause* 2008, 15: 51-58
- Rostock M, Fischer J, Mumm A, Stammwitz U, Saller R, Bartsch HH. Black cohosh (Cimicifuga racemosa) in tamoxifen-treated breast cancer patients with climacteric complaints - a prospective observational study. *Gynecol Endocrinol* 2011, 27(10): 844-8.
- Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002, 288(3):321-33
- Ruhlen RL, Haubner J, Tracy JK, Zhu W, Ehya H, *et al.* Black cohosh does not exert an estrogenic effect on the breast. *Nutr Cancer* 2007, 59(2): 269-277
- Schellenberg R, Saller R, Hess L, Melzer J, Zimmermann C, Drewe J, *et al.* Dose-dependent effects of the Cimicifuga racemosa extract Ze 450 in the treatment of climacteric complaints: a randomized, placebo-controlled study. *Evid Based Complement Alternat Med* 2012, doi 10.1155/2012/260301

- Schmidt M, Polasek W, Käufeler R. Efficacy and safety of Black Cohosh (*Cimicifuga racemosa*, Cimifemin) in menopause discomfort: surveillance study in practical terms. *Journal für Menopause* 2005, 12(1): 27-32
- Schneider HPG, Rosemeier HP Schnitker J, Gerbsch S, Turck R. Application and factor analysis of the menopause rating scale [MRS] in a post-marketing surveillance study of Climen. *Maturitas* 2000, 37: 113-124
- Schneider HPG, Heinemann LAJ, Rosemeier HP, Potthoff P, Behre HM. The Menopause Rating Scale (MRS): comparison with Kupperman index and quality-of-life scale SF-36. *Climacteric* 2000, 3: 50-58
- Seidlová-Wuttke D, Jarry H, Becker T, Christoffel V, Wuttke W. Pharmacology of *Cimicifuga racemosa* extract BNO 1055 in rats: bone, fat and uterus. *Maturitas* 2003, 44(1): 39-50
- Shahnazi M, Nahaee J, Mohammad-Alizadeh-Charandabi S, Bayatipayan S. Effect of black cohosh (*Cimicifuga racemosa*) on vasomotor symptoms in postmenopausal women: a randomized clinical trial. *J Caring Sci* 2013, 2(2):105-113, doi 10.5681/jcs.2013.013
- Shams T, Setia MS, Hemmings R, McCusker J, Sewitch M, Ciampi A. Efficacy of black cohosh-containing preparations on menopausal symptoms: a meta-analysis. *Altern Ther Health M* 2010, 16(1): 36-44
- Simpson B. Hot flash pharmacotherapy in breast cancer survivors: a literature review. *CPJ/RPC* 2004, 137(3): 36-45
- Spangler L, Newton KM, Grothaus LC, Reed SD, Ehrlich K, et al. The effects of black cohosh therapies on lipids, fibrinogen, glucose and insulin. *Maturitas* 2007, 57: 195-204
- Stoll W. Phytotherapeutikum beeinflusst atrophisches Vaginalepithel [Phytopharmacon influences atrophic vaginal epithelium. Double blind study – *Cimicifuga* vs. estrogenic substances.]. *Tpk Therapeutikon Sonderdruck Heft* 1987, 1: 2-15
- Stolze H. Der andere Weg, klimakterische Beschwerden zu behandeln. [An alternative to treat menopausal complaints.] *Gyne, Fachzeitung für praktische Frauenheilkunde und allgemeine Medizin* 1/82; Sonderdruck Januar 1982
- Uebelhack R, Blohmer JU, Graubaum HJ, Busch R, Gruenwald J, Wernecke KD. Black cohosh and St. John's wort für climacteric complaints: a randomized trial. *Obstet Gynecol* 2006, 107(2 Pt 1):247-255
- Umland EM. Treatment strategies for reducing the burden of menopause-associated vasomotor symptoms. *J Manag Care Pharm* 2008, 14(3 Suppl):14-19
- USP 39, The United States Pharmacopeia NF 34, Vol. 4, The National Formulary, Official from May 1, 2016. Dietary Supplements: Black Cohosh, pp 986-990
- van Breemen RB, Liang W, Banuvar S, Shulman LP, Pang Y, Tao Y, et al. Pharmacokinetics of 23-epi-26-deoxyactein in women after oral administration of a standardized extract of black cohosh. *Clin Pharmacol Ther* 2010, 87(2): 219-225
- Vermes G, Bánhidý F, Acs N. The effects of remifemin on subjective symptoms of menopause. *Adv Ther* 2005, 22(2): 148-154
- Vorberg G. Therapie klimakterischer Beschwerden. *ZFA, Zeitschrift für Allgemeinmedizin* 1984, 60(13): 626-629

Warnecke G. Beeinflussung klimakterischer Beschwerden durch ein Phytotherapeutikum. *Med Welt* 1985, 36: 871-874

Wuttke W, Gorkow C, Seidlova-Wuttke D. 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): 185-196

Wuttke W, Seidlova-Wuttke D, Gorkow C. The *Cimicifuga* preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. *Maturitas* 2003, 44(1): 67-77

Zava DT, Dollbaum CM, Blen M. Estrogen and progestin bioactivity of foods, herbs, and spices. *P.S.E.B.M.* 1998, 217: 369-378

References, which have been evaluated but not included into the assessment report

Hirschberg AL, Henneicke-von Zepelin HH, Liske E, Friede M. Clinical study of the drug safety of black cohosh on breast epithelial cell proliferation and mammographic breast density in postmenopausal women. Abstracts of free communications 0174. *Climacteric* 2005, 8(2): 128

Qiu F, McAlpine JB, Krause EC, Chen SN, Pauli GE. Pharmacognosy of black cohosh: the phytochemical and biological profile of a major botanical dietary supplement. *Prog Chem Org Nat Prod* 2014, 99:1-68

Teschke R, Bahre R, Fuchs J, Wolff A. Black cohosh hepatotoxicity: quantitative causality evaluation in nine suspected cases. *Menopause* 2009, 16(5): 956-965

Teschke R, Schwarzenboeck A. Suspected hepatotoxicity by *Cimicifugae racemosae* rhizoma (black cohosh, root): critical analysis and structured causality assessment. *Phytomedicine* 2009, 16: 72-84

Teschke R, Schwarzenboeck A, Hennermann KH. Causality assessment in hepatotoxicity by drugs and dietary supplements. *Br J Clin Pharmacol* 2008, 66(6): 758-766

Teschke R, Schwarzenboeck A, Schmidt-Taenzler W, Wolff A, Hennermann KH. Herb induced liver injury presumably caused by black cohosh: A survey of initially purported cases and herbal quality specifications. *Ann Hepatol* 2011, 11: 249-259