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Critical evaluation of the safety of *Cimicifuga racemosa* in menopause symptom relief

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Abstract

Objective: This comprehensive review examines the safety of *Cimicifuga racemosa* for the treatment of menopause symptoms, particularly in populations in which conventional menopause treatment regimens, including estrogen replacement, are contraindicated.

Design: An extensive database of information on *Cimicifuga*, which included all published literature pertaining to preclinical and clinical safety of various forms of *Cimicifuga*, the FDA and World Health Organization adverse-event reporting systems, monographs, compendia, internal unpublished data from a major manufacturer, foreign literature, and historical anecdotal reports, was reviewed, and findings pertaining to the safety of *Cimicifuga* use for menopause treatment were reported.

Results: Uncontrolled reports, postmarketing surveillance, and human clinical trials of more than 2,800 patients demonstrate a low incidence of adverse events (5.4%). Of the reported adverse events, 97% were minor and did not result in discontinuation of therapy, and the only severe events were not attributed to *Cimicifuga* treatment.

Conclusions: Although the effects of *Cimicifuga* may be dependent on the specific extract preparation, this review clearly supports the safety of specific *Cimicifuga* extracts, particularly isopropanolic preparations, for use in women experiencing menopausal symptoms and as a safe alternative for women in whom estrogen therapy is contraindicated.

Key Words: Black cohosh – *Cimicifuga racemosa* – Menopause – Safety – Toxicology.

Menopause, a naturally occurring phenomenon in women between the ages of 40 and 60 years, represents the cessation of menstrual cycles and corresponding loss of estrogen and progesterone secretion. A significant number of women entering menopause exhibit symptoms—including hot flashes, night sweats, irritability, depression, anxiety, and sleep disorders—that can lead to significant disruptions in the course of daily life. In extreme cases, such symptoms lead women to seek medical attention.

Hormone replacement therapy (HRT), a commonly prescribed treatment for managing the long-term effects of lowered estrogen and progestogen levels, is often recommended for relieving distressing menopausal symptoms. Although estrogen therapy has beneficial effects on bone health and osteoporosis[1] and has been used successfully for decades to treat the estrogen deficiency symptoms of menopause, known side effects associated with HRT include bloating, breast tenderness, cramping, irritability, depression, breakthrough bleeding, or a return to monthly periods. Other potential side effects of HRT, which cause many women to seek alternatives, include increased risk of endometrial, ovarian, and breast cancers[2,3] from hormone-induced, estrogen receptor-positive cell proliferation.[4] Risk of cancer associated with HRT is particularly high in women over the age of 55 years and in those who have used HRT for more than 5 years.[3,5] On the basis of this risk and findings from the Women's Health Initiative, the US Preventive Services Task Force published a recommendation against the routine use of HRT for the prevention of chronic conditions in postmenopausal

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women.[6] Therefore, women with, or at high risk for, estrogen-sensitive cancers are increasingly seeking safe and effective alternative therapies for the treatment of menopausal symptoms. Coupled with recent findings that HRT may not provide cardiovascular benefits as previously indicated,[7] the risks associated with HRT have led many women to question whether such therapy is right for them.

Although a number of dietary supplements are available for the treatment of menopausal symptoms, including dong quai, evening primrose, ginseng, licorice, chasteberry, St. John's wort, red clover, vitamin E, and black cohosh,[8] many people have concerns regarding safety, purity, and quality of such substances.[9] Of these alternative therapies, the rhizome of black cohosh (*Cimicifuga racemosa* (L.) *Nutt.*), which has a long tradition of use for various clinical indications, is the most widely studied herb in menopause treatment.[10] It should be noted that other "alternative" treatments for menopausal symptoms are available by prescription, including clonidine and selective serotonin reuptake inhibitors.

C. racemosa, native to eastern North America and found from Georgia north to Ontario and west to Arkansas and Wisconsin, is an erect perennial that grows in forests.[11] The leafy stalks and floret sprout from a rhizome, the organ from which commercially available extracts are derived. Black cohosh, a member of the buttercup family (Ranunculaceae), was first classified by Linnaeus as *Actaea racemosa* and later reclassified as *Cimicifuga* by Pursh. It was temporarily placed under the genus *Macrotys*, which led many eclectic practitioners to use *macrotys* as the common name of trade. However, the herb has been referred to by numerous names throughout history, including *Actaea racemosa*, *Cimicifuga serpentaria*,[12-14] *Botrophys racemosa*,[15] black cohosh,[13,14] *C. racemosa,*[13] *Macrotys racemosa*,[15,16] macrotys,[17] black snakeroot,[12,14] and *C. racemosa* (L) *Nuttall*.[18] *Squaw root,* another term used to refer to black cohosh (*Cimicifuga*), has also been used to refer to blue cohosh (*Caulophyllum thalictroides*), an herb with a similar name[15,19] but with a very different and distinct therapeutic profile.[20] The use of ambiguous terminology in early literature reports highlight the need for caution when comparing reports of medicinal herbs. Geographic variations in plant species may also create confusion between actual species and terminologies of medicinal plants.

Native Americans have long recognized the beneficial effects of *Cimicifuga*, using the herb for the treatment of general malaise, kidney aliments, malaria, rheumatism, sore throat, and menstrual cramps and for ease of labor. US colonists also used the herb for treatment of amenorrhea, bronchitis, chorea, dropsy, fever, hysteria, itch, lumbago, nervous disorders, snakebite, yellow fever, and uterine disorders.[21] Literature reports of *Cimicifuga* use date back as early as 1801, when eclectic physicians reported the use of *Cimicifuga* for relief of pain associated with acute rheumatism, neuralgia,[16,18] influenza, smallpox,[18] labor and postpartum pains,[17] headache and cough,[18] and chorea[12] and other nervous system disorders[22] as well as to encourage natural intermittent uterine contractions during labor.[18,23]

Although early reports indicate the effectiveness of *Cimicifuga* for a variety of indications, *Cimicifuga* extracts are used today primarily for the treatment of menopausal symptoms. Clinical evaluations[24-31] support early reports suggestive of *Cimicifuga* use for relief of menopausal complaints.[32]

Since its introduction as a medicinal agent, clinical effects of *Cimicifuga* have been noted in various preparations, including rhizome powders, tinctures, infusions, and fluid or solid extracts.[33] Early reports suggest *Cimicifuga* efficacy is dependent upon the type of formulation,[13,18,22,34] with tinctures or extracts of the rhizome made with alcohol exhibiting greater effect than aqueous preparations and infusions.[13,33]

Today, a variety of *Cimicifuga* preparations, including isopropanolic and ethanolic extracts, are widely available. The proprietary isopropanolic preparation of *Cimicifuga*, Remifemin (developed and produced by Schaper & Brümmer, Salzgitter, Germany, and marketed in the United States by GlaxoSmithKline Consumer Healthcare, Pittsburgh, PA) has been widely studied, thus providing supportive evidence for the safety of *Cimicifuga* extracts in menopause treatment. On the basis of clinical experiences with commercial products, the currently recommended dose of *Cimicifuga* is a 40% to 60% ethanol or isopropanol extract in a daily dose of 40 to 80 mg herbal drug that is quality controlled for quantity of triterpene glycosides.[35] A recently published study[31] demonstrated that there is no superiority of a high dose of *Cimicifuga* (127 mg/day) over the currently recognized 40 mg/day dose, thus supporting the current recommended extract dose. Despite these findings, many have advocated the use of a higher daily dose (80 mg) on the basis of the safety profile of *Cimicifuga*.

As both the indications for use and methods for preparation have changed since early reports of *Cimicifuga* use, it is important to distinguish the safety and efficacy findings of modern *Cimicifuga* extracts from reports on earlier extracts. This safety review specifi-

cally addresses the safety of *Cimicifuga* use in the general menopausal population, as well as in specific patient groups. To address concern regarding the safety risks of *Cimicifuga* as an alternative to HRT, we emphasize studies investigating the estrogenic activity of the medicinal herb on estrogen levels and in estrogen-sensitive populations, including patients at risk for breast cancer.

METHODS

As is customary when evaluating safety data, we have considered all types of evidence including uncontrolled reports, postmarketing surveillance, preclinical studies, and controlled clinical evaluations (published and unpublished) to assess the safety of *Cimicifuga* therapy in women with menopausal complaints. Literature was identified through a search of MEDLINE, BIOSIS, EMBASE, and SciSearch for all published literature pertaining to preclinical and clinical safety of various forms of *Cimicifuga*. In addition, we reviewed the Food and Drug Administration (FDA) and World Health Organization (WHO) adverse-event reporting systems, monographs, compendia, internal unpublished data from Schaper & Brümmer, and foreign literature, as well as collected historical, anecdotal reports. Further, we conducted tree-searching to identify other relevant articles. All articles identified were reviewed in an effort to conduct a comprehensive safety assessment.

Although we consider historical anecdotal reports of the safety of black cohosh, our analyses rely more heavily on more recent data generated with the commercially available *Cimicifuga* extracts.

RESULTS

Historical reports on safety

Until the late 1800s, the safety of various *Cimicifuga* preparations was determined through experience. The side effect profiles widely cited today for *Cimicifuga* are largely based on early reports with large doses of the crude herb and, therefore, lack relevance to currently marketed formulations. Original doses ranged from between 1 and 60 grains, corresponding to approximate doses of 65 mg to 4.0 g crude herb, taken several times a day.[12,13,18,22] Today, the recognized dose is 40 mg of *Cimicifuga* extract per day;[35] however, *Cimicifuga* capsules, tinctures and fluid extracts are readily available on the market that provide doses of up to 500 mg, or more, of crude herb. Early reports have reported that unspecified large doses of *Cimicifuga*, presumably those larger than the traditionally prepared doses of between 1 and 60 grains, may cause transient effects, including dizziness,[36] vertigo, dimness of vision, and a depression of the pulse.[13,37] Other early reports of macrotys suggest that large doses of the herbal preparation [apparently, more than 2 teaspoons (10 mL) of tincture (unspecified concentration) every 3 hours] are associated with exhaustion and sickness of the stomach.[38] Large doses of *Cimicifuga* in pregnant women are reported to induce abortion.[37,39] Despite this reported reaction to unspecified large doses, early reports suggest that *Cimicifuga* exerts only weak "oxytoxic" (uterine stimulant) effect.[39] However, further research is warranted to determine the safety of current black cohosh preparations during pregnancy.

Clinical effects of *Cimicifuga* for treatment of persistent neuralgia have been noted to be most beneficial after *Cimicifuga* doses large enough to induce a "full feeling" in the head accompanied by a dull headache.[38] Whereas a headache could be considered an adverse reaction, it appears that early physicians considered this event a sign of clinical efficacy.

Animal studies evaluating the safety of *Cimicifuga* were introduced in 1887, with whole-animal investigations of the effects of *Cimicifuga* on frogs, rabbits, and dogs at extract concentrations of approximately 1.875, 5.625, and 10 mL, respectively.[40] These early in vivo studies confirm the findings of Davis,[13] suggesting that *Cimicifuga* exerts a sedative effect, likely through the central nervous system.[36]

In 1932, Macht and Cook performed an experimental investigation of the fluid extract of *Cimicifuga* and of the isolated constituent, cimicifugin, to determine the effects of these preparations on various body functions.[41] In contradiction to earlier animal data and use experiences, Macht and Cook's experiments suggest that *Cimicifuga* exerts very little sedative effect on the brain and neuromuscular functions of rats. Macht and Cook also noted adverse effects of the *Cimicifuga* preparation, including a relaxing and paralyzing effect on intestinal and uterine muscles, indicating a depressant and toxic property of the drug. Additionally, Macht and Cook noted a marked depression of respiration and circulation after intravenous administration of *Cimicifuga*, the latter of which confirms earlier observations of *Cimicifuga*.[13,40] These ex vivo and animal studies provide some of the earliest scientific research available on *Cimicifuga*; however, the adverse effects noted by Macht and Cook are of limited relevance for oral human consumption at the doses typically used today.

Adverse events associated with *Cimicifuga* that are relevant to human use may be dependent on the specific

TABLE 1. *Adverse events to Cimicifuga as reported to the US Food and Drug Administration*

Adverse events as reported	Name of product	Manufacturer	Ingredients
Heart attack	The Edge	Adonis Health Products (Lawrence, KS)	Ma-huang, saw palmetto, wild yam, guarana, fo-ti, skullcap, black cohosh, licorice root, royal jelly, bee pollen, L-tryptophan, chromium, glandulars, amino acids, lipotropics, sterols, calcium, magnesium, octacosanol, RNA, DNA, others
Flushing of skin, swelling of extremities and face, headache	Jenasol Circulation Plus	Jenasol, Inc (Hallandale, FL)	Ginkgo biloba extract, butcher's broom, cayenne pepper, ginger root, niacin, goldenseal, black cohosh
Pregnant female with platelet count 55,000, bleeding time of 15 min, and hemoglobin of 8.2	5-W	Nature's Sunshine Products (Provo, UT)	Black cohosh, squawvine, dong-quai, butcher's broom, red raspberry leaf
Increasing anxiety, anger, and stress	Eight Combination	Nature's Sunshine Products (Provo, UT)	Willow bark, black cohosh root, capsicum, valerian root, ginger root, hops flowers, wood betony, devil's claw root
Headaches, blurred vision, lightheaded, dizziness	Nature's Secret AM/PM Ultimate Cleanse with Multi-Fiber and Multi-Herb	Nature's Secret/4Health, Inc (Los Angeles, CA)	Hawthorn berry, red clover, skullcap, black cohosh, slippery elm, echinacea, ginkgo biloba, cascara sagrada, shattered cell wall chlorella, lactobacilli, fenugreek, yarrow, horsetail, others
Diarrhea, progressive proximal muscle weakness, nephrotic syndrome	Internal Cleansing System Multi-Herb Formula	Harmony Formulas, Omni Nutraceuticals (Los Angeles, CA)	Fenugreek, yarrow flower, cat's claw, hawthorn berry, Australian herb, licorice root, marshmallow, red clover, red raspberry root, skullcap, burdock root, chickweed, mullein, black cohosh, Irish moss, kelp, slippery elm bark, echinacea, ginkgo, others
Severe chest pain, "high" serum digoxin level	Nature's Way Ex-Stress	Nature's Way Products, Inc (Springville, UT)	Skullcap, wood betony, black cohosh, hops, valerian, cayenne
"Exhausted all the time"	Unspecified BioSlim product #2	Medicus Formulas, Inc (Woodland Hills, CA)	Vitamin C, vitamin B6, coenzyme Q10, glucomannan, chormium nicotinate, atractylodes, astragalus, bupleurum, angelica sinensis, glycyrrhiza uralensis, citrus peel, *Cimicifuga,* jujube, panax ginseng, sargassum, laminaria, scutellaria, others
Headaches and high blood pressure	Black cohosh tablets	Enzymatic Therapy, Inc (Green Bay, WI)	Black cohosh

herbal preparation. The freshness of the plant, for example, has been implicated as a factor determining the estrogen-like effects of *Cimicifuga*, as noted by von Gizycki.[16,33,42,43] Because of the variety of indications and preparations, early reports of adverse events may not accurately reflect the current safety profile of *Cimicifuga* for treatment of menopausal symptoms.

Uncontrolled reports

In the United States, the FDA maintains the Special Nutrition Adverse Events Monitoring System (SN/AEMS), a database of adverse events reported voluntarily by consumers and healthcare professionals. Although the database may be suggestive of adverse events noted during postmarketing surveillance of a product, the database is not an accurate measure of all adverse events, and there is no certainty that a reported adverse event can be attributed to a particular product or ingredient. A search of the SN/AEMS database for adverse reactions to *Cimicifuga* (using search terms *Cimicifuga* and *black cohosh*) revealed nine adverse events reported on or before October 20, 1998[44,45] (Table 1). Only one of the nine events (headaches and high blood pressure) was reportedly due to *Cimicifuga* as a solo agent (black cohosh tablets, Enzymatic Therapy Inc, Green Bay, WI). Other reported events were reported as a result of combination herbal therapies that included *Cimicifuga*. Because of the nature of such reporting, however, it is impossible to evaluate and verify actual exposure.

The WHO Collaborating Center for International Drug Monitoring also maintains a comprehensive database of adverse reactions reported worldwide. The WHO Collaborating Center receives summary clinical reports, with limited medical detail, that highlight indi-

TABLE 2. *Adverse events by organ system reported to World Health Organization Collaborating Center for International Drug Monitoring, July 2000*

Organ system	Number of adverse event reports
Abdominal pain[a]	1
Arthralgia	1
Back pain	1
Breast enlargement[a]	1
Breast pain (female)[a]	1
Depression	1
Dermatitis	1
Endometiral hyperplasia	2
Epistaxis	1
Fertility decreased (female)	1
Genital neoplasm malignant	1
Hemorrhage rectum	1
Hepatic enzymes increased	1
Hepatic failure	1
Hepatitis	1
Hypertension	1
Hypertonia	1
Intermenstrual bleeding	1
Jaundice	1
Malaise	1
Menstrual disorder	2
Nausea[a]	1
Nephritis interstitial	1
Pruritus	1
Purpura	1
Purpura thrombopenic throm	1
Rash	1
Rash erythematous	2
Synovitis	1
Thrombosis venous arm	1
Urticaria	1
Vaginal hemorrhage	1
Total	35

[a]Symptoms of the corresponding gynecological syndromes such as premenstrual syndrome, dysmenorrhea, and menopausal complaints, all of which are indications of *Cimicifuga* use according to the German Commission E monograph.

vidual suspected adverse reactions to pharmaceutical products. A search of this database for all reported adverse reactions for *Cimicifuga*, including all salts/esters and *Cimicifuga* root, as of July 31, 2000, revealed a total of 35 adverse reactions.[46] The reported reactions were primarily general symptoms and were not concentrated on a particular organ system (Table 2). Although it is impossible to accurately determine the actual exposure to *Cimicifuga* in these cases, the incidence of only 35 adverse events from a variety of products containing *Cimicifuga* alone or in combination with other ingredients suggests a good tolerability of *Cimicifuga* preparations.

The Commission E, a German governmental body that reviews the use and safety of herbal products, published a positive monograph on *Cimicifuga*, supporting that the herb is a safe nonprescription drug for "premenstrual discomfort, dysmenorrhea, or climacteric [menopausal] ailments."[47] The German Commission E does not identify any drug interactions with *Cimicifuga* treatment, and there are no known adverse drug interactions between isopropanolic extracts and other active substances. However, adverse events reported to the FDA and WHO Collaborating Center highlight the possibility of interactions between *Cimicifuga* and other herbal products, thus warranting the use of caution when combining herbal products. One case report further highlights the need for caution and indicates individual variations in adverse responses to herbal combinations. A 45-year-old woman who combined separate bottled products of *Cimicifuga*, *Vitex agnus-castus* (Nature's Herbs, American Fork, UT) and evening primrose oil to regulate her menstrual cycle reported nocturnal seizures after 4 months of self-treatment.[48] The patient reported experiencing three generalized tonic-clonic seizures within 3 months of consuming this combination of herbs. Medical history and workup were negative; however, the patient reported consuming alcohol within 48 hours of each episode. The herbal product was discontinued, and she was prescribed carbamazepine, without any further episodes of seizure. The report notes that the patient's sister used the same self-treatment regimen for 1 to 2 years without incidence of side effects.

Despite early suggestions of the safety of *Cimicifuga* in pregnant women, recent reports discourage the use of *Cimicifuga* during pregnancy and lactation because possible effects on the fetus have not been adequately studied.[49] As such, the *American Herbal Products Association's Botanical Safety Handbook*[50] suggests that *Cimicifuga* not be taken during pregnancy or while nursing. Contraindications for use of *Cimicifuga* during pregnancy may stem from a report of a mother who gave birth after a combination of *Cimicifuga* and blue cohosh (*Caulophyllum thalictroides*) was used to induce labor; the child was born without spontaneous breathing and subsequently suffered brain hypoxia.[51] The contribution of *Cimicifuga* in this case is improbable, as blue cohosh has been implicated in a similar case report in which an infant suffered an anterolateral myocardial infarction, possibly related to an overdose. In this case, the mother was taking blue cohosh at twice the recommended dose for 3 weeks during the third trimester of pregnancy.[52] Unlike black cohosh, there is little question that blue cohosh contains some potentially harmful constituents; the plant is featured in standard textbooks on North American poisonous plants. Although there is little scientific data to support the claim, *Cimicifuga* is not suggested for use in nursing mothers based on the possible maternal transfer of

TABLE 3. *Post marketing studies of Cimicifuga safety in menopause treatment*

Reference	Study parameters (subjects exposed to extract)	*Cimicifuga* formulation	Treatment duration	Safety-related outcomes
Stolze, 1982[24]	629 menopausal women	Ethanolic extract (Remifemin solution)	8-week open study	7% unspecific short-lived side effects (none that required discontinuation of therapy)
Nesselhut and Liske, 1999[53]	40 menopausal women	Isopropanolic extract (Remifemin tablets)	12-week study	No reported adverse events; no evidence of estrogenic activity of extract

Cimicifuga during breast-feeding and on its possible action, including stomach upset and colic, in breast-fed infants.[49] As such, the WHO monograph on *C. racemosa* cites pregnancy and lactation as contraindications.[46]

Postmarketing surveillance

Postmarketing studies support the safety of *Cimicifuga* extracts (Table 3). In the largest postmarketing surveillance study of *Cimicifuga* solution (ethanolic extract; Remifemin), 629 menopausal women were treated with the *Cimicifuga* extract for 8 weeks. In this multicenter, open study, only 7% of the patients developed mild, transitory side effects, predominantly gastrointestinal in nature, none of which required discontinuation of therapy.[24]

A postmarketing surveillance study of isopropanolic *Cimicifuga* tablets (136 mg drug daily for 3 months) administered to 40 postmenopausal women with menopausal complaints and an endometrial status typical for menopause evaluated the safety of this extract over a 3-month period.[53] Of the 28 patients who completed the study (12 did not return to the control examination without stating a reason), the isopropanolic extract did not significantly affect vaginal cell status or reproductive hormones [luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E_2), and prolactin] as compared with baseline. Likewise, there was no increase in endometrial thickness in comparison to baseline. In the absence of a positive control, the significance of this finding is unclear. However, based on the lack of adverse events in this 3-month study, there is preliminary evidence supporting the safety of the isopropanolic extract (Remifemin).

The postmarketing experience of *Cimicifuga* is reflected in the German Commission E monograph as well as in the World Health Organization monograph on *Cimicifuga*.[54]

Preclinical safety

Several in vitro and in vivo preclinical studies have been conducted to investigate the effects of *Cimicifuga* extracts (Tables 4 and 5) on a variety of tissues.

To examine the cytotoxic and mutagenic effects of *Cimicifuga* extracts, the well-established in vitro screening method developed by Ames[55] and Ames et al[56,57] was used. The Ames test uses a salmonella/microsome assay to detect mutations caused by chemical agents with a reasonable level of reliability. The Ames toxicology study conducted by Schaper & Brümmer (unpublished internal research, 1990) found no evidence of genetic mutation caused by isopropanolic *Cimicifuga* extract (Remifemin) at doses ranging from 0.32 to 1000 μg/plate. This study demonstrates that the isopropanolic extract does not have a dose-dependent mutagenic effect, nor does it induce biologically relevant increases in mutation rates as compared with the negative (solvent) and positive controls (known mutagenic agents).

Other study groups have validated the lack of mutagenic effects of *Cimicifuga*. Hemmi and colleagues[58] tested the effect of *Cimicifuga* (formulation unspecified) on the uptake of labeled thymidine into phytohemagglutinin-stimulated lymphocytes and mouse lymphosarcoma L-5178 cells and demonstrated that *Cimicifuga* selectively inhibits the uptake of uridine, adenosine, and thymidine without inhibiting mitosis or DNA synthesis.

A long-term (26 weeks) in vivo study of isopropanolic *Cimicifuga* (Korn, Schaper & Brümmer, internal research, 1991) was conducted to determine the toxicity of this extract on various tissues and physiologic systems. This study evaluated the effects of an orally administered Remifemin granulate, which contains the active *Cimicifuga* constituents, to female Wistar rats for 26 weeks in daily doses of 250, 1800, or 5,000 mg/kg body weight, thus reflecting a safety factor up to 740-fold in comparison to the recommended therapeutic dose. The treated animals were compared with animals treated with 4,982 mg/kg of the Remifemin additive, a control that mimics the vehicle of the test substance. After an 8-week recovery period, the experimental animals were evaluated on a series of clinical parameters and laboratory measures (Korn, Schaper & Brümmer, internal research, 1991).

TABLE 4. *In vitro studies highlighting* Cimicifuga *safety*

Reference	Study parameters	*Cimicifuga* formulation	Safety-related outcomes due to *Cimicifuga*
Hemmi et al, 1979[58]	Phytohemagglutinin-stimulated lymphocytes and mouse lymphosarcoma L-5178 cells	Unique extract formulations not specified	No cytotoxic or inhibitory effects on cell growth; no inhibitory effect on DNA synthesis
Schaper & Brümmer, internal report (1990)	Histidine auxotrophlic mutants of *Salmonella typhimurium*	Isopropanolic extract	No genetic mutation; no dose-dependent doubling or biologically relevant increase in mutations
Nesselhut et al, 1993[66]	Mamma carcinoma cell line MDA MB 435S	Isopropanolic extract	No growth-stimulating effects
Dixon-Shanies and Shaikh, 1999[68]	T-47D and MCF-7 cells (estrogen receptor–positive cell line)	Ethanolic extract	No growth-stimulating effects
Liu et al, 2001[70]	Various in vitro assays	Methanolic extract	Lack of estrogen receptor binding and estrogenic bioactivity
Zierau et al, 2002[71]	MCF-7 cells (estrogen receptor–positive cell line); MVLN cells (estrogen-inducible cells)	Ethanolic extract and isopropanolic extract	Lack of estrogenic effect on cell proliferation or gene expression
Bodinet and Freudenstein, 2002[69]	MCF-7 cells (estrogen receptor–positive cell line)	Isopropanolic extract	Inhibition of cell proliferation
Löhning et al, 2000[a,b]	MCF-7 cells (estrogen receptor–positive cell line)	Ethanolic extract	Low concentrations induced estrogenic effects
Jarry et al, 1985, 1999[64,65,b]	Estrogen receptor assay	Ethanolic extract	Estrogen receptor binding causing activation of the transcription of estrogen-regulated genes

[a]Löhning A, Verspohl E, Winterhoff H. *Cimicifuga racemosa:* in vitro findings using MCF-7 cells [Poster]. *Phytopharmakaforschung* 1998;72–73.
[b]Data are contradictory of lack of estrogenic effect of *Cimicifuga.*

Animals in both the control and isopropanolic extract dose groups appeared to be healthy, with normal motor and sensory activity and body weight development throughout the study period. Reflex, ophthalmoscopic, and auditory examinations did not reveal any adverse findings related to the administration of the test article (Korn, Schaper & Brümmer, internal research, 1991). Three animals (two in the control group and one in the extract treatment group) died or were in moribund condition throughout the treatment period as a result of accidental (intratracheal) administration. Animals in the extract test group were found to consume slightly more food than the control animals, a finding that may represent a pharmacodynamic effect of the test article. Histopathological examinations of the test animals, however, were unremarkable and noted no estrogen-like morphological changes in organs or tissues after 6 months of treatment. Relative liver weights, however, were slightly increased in the animals treated with the high dose of extract, and significant changes in the heart and ovary weights of the high-dose group were also noted. These observed values returned to normal after 8 weeks of recovery. Clinical chemistry analyses revealed no treatment-related changes at any point during the investigation, and urinalysis did not reveal any notable treatment-related changes. Animals in both the treatment and control groups showed augmented immune reactions; however, there was no statistical significance between such responses (Korn, Schaper & Brümmer, internal research,1991).

Korn (Schaper & Brümmer, internal research, 1991) concludes that the slight changes in body weights and food consumption are not toxic effects and that the lack of adverse effects at doses at or below 1,800 mg/kg body weight over the 6-month period supports the safety of the isopropanolic *Cimicifuga* extract. Toxicity studies of this type and duration, which provide important predicting potential in determining long-term safety in humans,[59] support the use of *Cimicifuga* preparations beyond 6 months.

To fully evaluate the herb's clinical action for menopause treatment, it is important to examine its effect on estrogen-sensitive organs. An early animal study of *Cimicifuga* preparations on the uterus of mice[60] suggests that the herb does not adversely affect this organ. Likewise, a study on the uterine growth of immature mice and proliferation of the vaginal epithelium of ovariectomized rats[61] supports the notion that *Cimicifuga* extracts do not exert estrogenic effects. In this study, a large dose of ethanolic *Cimicifuga* (600 mg/kg)

TABLE 5. *In vivo studies highlighting Cimicifuga safety*

Reference	Study parameters	Treatment duration	*Cimicifuga* formulation	Safety-related outcomes due to *Cimicifuga*
Korn, 1991 (Schaper & Brümmer internal report)	120 female Wistar rats	6 mo	Isopropanolic extract	No evidence of toxicity
Siess, 1960[60]	Mice	Not specified	Ethanolic extract	No activity on uterus
Einer-Jensen et al, 1996[61]	22 immature mice/ovariectomized rats	3 d	Ethanolic extract	No vaginotrophic effects; no uterine growth or vaginal epithelium growth
Nisslein and Freudenstein, 2000[a]	30 ovariectomized rats	5 wk	Isopropanolic extract	Inhibitory effect on hormone-regulated bone resorption
Freudenstein, 2000[62]	75 ovariectomized Sprague-Dawley rats with DMBA-induced mammary gland tumors	5–9 wk	Isopropanolic extract	No effect on prolactin, FSH, and LH levels No stimulation of mammary tumor growth No effect of estrogen-sensitive organs
Földes, 1959[83] [b]	62 ovariectomized rats	3 d	Isopropanolic extract	Increased in uterus size in mice but not in rats
Jarry et al, 1985, 1999[64,65] [b]	Ovariectomized rats	7 d	Ethanolic/ methanolic extract	Reduction in LH levels; no increase in uterus weight
Jarry and Harnischfeger, 1985[63] [b]	Ovariectomized rats	3–14 d	Methanolic extract	Reduction in LH levels; no change in FSH or prolactin levels

LH, luteinizing hormone; FSH, follicle-stimulating hormone; DMBA, 12-dimethylbenz[a]anthracene.
[a]Nisslein T, Freudenstein J. Effects of black cohosh on urinary bone markers and femoral density in an OVX-rat model. Presented at: World Congress on Osteoporosis; June 15–18, 2000; Chicago, Illinois.
[b]Data are contradictory of lack of estrogenic effect of *Cimicifuga.*

administered orally or subcutaneously did not exert vaginotrophic effects on ovariectomized rats or uterotrophic effects on immature mice.

Similarly, a recent study[62] of ovariectomized Sprague-Dawley rats with 7,12-dimethylbenz[α]anthracene-induced mammary gland tumors shows that, unlike estrogen, *Cimicifuga* extract—in doses comparable to 1, 10, or 100 times the human therapeutic dosage—fails to induce mammary tumor development. The study investigators also noted a lack of estrogen-agonist effects on plasma hormone levels (prolactin, FSH, LH), estrogen-sensitive organ weights, and uterine tissue.

In contrast to the studies reviewed above, data from two studies of ovariectomized rats published in 1985 suggest that *Cimicifuga* causes a selective reduction of LH.[63-65] Findings suggestive of an estrogenic effect of *Cimicifuga* may be due to differences in study extraction techniques, extract preparation (ie, isopropanolic, ethanolic, or methanolic), active plant ingredients obtained, cell culture media, and experimental conditions or procedures. It should be noted that the same research team performed both of these studies and that more recent research has not been able to duplicate these results.

Studies using estrogen or progesterone receptor-positive human breast cancer cell lines MCF-7, MDA-MB-435S, and T-47D[66-69] and various in vitro assays[70] demonstrate that *Cimicifuga* extracts do not induce estrogenic effects on breast tissue or mammary tumors. In fact, these studies show a consistent inhibitory effect of the isopropanolic *Cimicifuga* extract on estrogen receptor-positive cancer cells. *Cimicifuga* extract (10^{-3}-10^{-5} dilutions) has been shown to significantly inhibit MCF-7 cell proliferation in estrogen-deprived conditions under test conditions in which estrogen treatment induces proliferation.[69] Bodinet and Freudenstein[69] have shown that, in the presence of estrogen, isopropanolic *Cimicifuga* extract inhibits estrogen-induced proliferation of estrogen receptor-positive cells. In addition, *Cimicifuga* was found to enhance the inhibitory effect of tamoxifen, a common breast cancer treatment drug, on estrogen receptor-positive cells.

Estrogenic and antiestrogenic activity of ethanolic and isopropanolic extracts of *Cimicifuga* on proliferation of MCF-7 cells and gene expression were recently tested by Zierau et al.[71] Estrogenic properties could not be detected in proliferation assays, in gene expression using an E_2-inducible yeast assay, or in assays with estrogen-inducible MVLN cells. In fact, in all three experimental systems, *C. racemosa* antagonized E_2-induced activities. Those investigators concluded that extracts of *C. racemosa* contain compounds that exert antiestrogenic activity. The replication of data by mul-

tiple teams reassures that *Cimicifuga* does not induce breast cancer cell proliferation.

Clinical safety

Clinical Evaluations

An evaluation of the total number of treated patients, adverse events, tolerability measures, and discontinuation rates reported in clinical trials was conducted to assess the tolerability of *Cimicifuga* extracts (Table 6). Of the clinical studies reviewed, a total of 2,140 women were treated with *Cimicifuga*, in doses ranging from 20 to 40 drops of ethanolic extract two times a day (corresponding to 48-140 mg crude drug) to 2 to 4 tablets (corresponding to 39-140 mg crude drug) isopropanolic extract per day for a period of 8 to 52 weeks. During the course of these clinical trials and observational studies, 5.4% of patients reported adverse events, 97% of which were minor and did not result in discontinuation of therapy. Of the three severe adverse events reported (one case of thrombophlebitis, in a patient suffering from varicosis;[29] one case of hysterectomy, recorded as an adverse event in a breast cancer survivor concurrently taking tamoxifen;[72] and one case of breast cancer recurrence, also in a breast cancer survivor concurrently taking tamoxifen[72]), the clinical investigators were unable to ascribe causation to the *Cimicifuga* extract.

A series of observational studies of *Cimicifuga* extracts in 1,465 women presenting with menopausal complaints, PMS, or other menstrual or hormonal disorders did not report any adverse effects related to treatment with isopropanolic or ethanolic *Cimicifuga* extract.[73-82] Another observational study of 41 patients treated with placebo followed by isopropanolic *Cimicifuga* extract reported a 7% incidence of stomach discomfort.[83] This study also suggests that *Cimicifuga* may exert a sedative effect; however, the adverse nature of this effect was not specified. In light of these data, the German Commission E monograph reports occasional gastric discomfort as the only noted treatment side effect.

Additional insight into incidence of gastrointestinal discomfort after *Cimicifuga* treatment is provided by the results of a 12-week open study.[26] In this study, 4 of the 50 women treated with 40 drops of an ethanolic *Cimicifuga* extract two times a day reported mild gastrointestinal disturbances. Similarly, gastric discomfort resulting in treatment withdrawal was reported in 8% of menopausal women treated with a *Cimicifuga* preparation (20 mg daily).[84] However, in the absence of a placebo arm, it is difficult to assess the actual level of ingredient-induced gastrointestinal adverse events, as such events are commonly reported.

The incidence of other adverse events is noted in several other clinical trials. In an open, uncontrolled study of an ethanolic *Cimicifuga* extract (48-140 mg drug per day), Daiber[25] reported two adverse events (one patient reported dry skin and another experienced hair loss). In a similar study, no adverse events or incompatibility reactions from treatment were reported; however, one patient discontinued treatment because of a lack of efficacy on psychological symptoms.[27] Similarly, a 6-month open trial of an isopropanolic *Cimicifuga* extract (two tablets twice per day) reported no dropouts or side effects from *Cimicifuga* treatment in 50 menopausal women previously treated with HRT.[28]

Controlled, double-blinded studies provide additional safety data for *Cimicifuga*. In a 12-week study, women between the ages of 45 and 58 years were treated with 0.625 mg of conjugated estrogens per day ($n = 30$), isopropanolic *Cimicifuga* extract per day (two Remifemin tablets twice daily; $n = 26$), or placebo ($n = 20$).[29] Of patients treated with the *Cimicifuga* extract, one patient, who was suffering from varicosis, discontinued therapy because of the aggravation of thrombophlebitis, a state that excluded her from continuing based on the study exclusion criteria. Twelve minor side effects were reported in the *Cimicifuga* treatment group; however, they did not lead to discontinuation of treatment. Reported side effects included "weight problems," mastodynia, heavy legs, "pepped up" feeling, headaches, and an increase of menopausal complaints that existed before treatment.

Recent studies of various *Cimicifuga* extracts also suggest a low incidence of adverse events. In a study of 100 premenopausal, perimenopausal, and postmenopausal women treated with an isopropanolic *Cimicifuga* extract (Remifemin; two tablets per day) for sweating and hot flashes, sleep disorders, depression, and irritation, the only reported adverse event was exanthema facialis without irritation (M. Todorova, unpublished data, 2001). In a study of 34 women treated with *Cimicifuga* extracts (4 mg triterpene glycosides daily for 6 months) for relief of menopausal symptoms, no side effects were observed; however, 4 patients discontinued therapy in favor of HRT.[85]

In a recent randomized clinical trial of 85 breast cancer survivors (59 of whom were concurrently receiving tamoxifen treatment) who were randomly assigned to isopropanolic *Cimicifuga* extract (20-mg tablet twice daily; $n = 42$) or placebo ($n = 43$) treatment groups,[72] eight minor adverse events (six in the *Cimicifuga*/tamoxifen group and two in the *Cimicifuga*/no tamoxifen

TABLE 6. *Clinical studies highlighting Cimicifuga safety in menopause treatment*

Reference	Study parameters (subjects exposed to extract)	*Cimicifuga* formulation	Treatment duration	Safety-related outcomes
Schotten, 1958[73]	22 women with menopausal complaints, PMS or pregnancy problems	Ethanolic extract (Remifemin solution)	Up to 6 mo	Adverse events were not observed
Földes, 1959[83]	41 menopausal women	Isopropanolic extract (Remifemin tablets)	No data on duration available	3 patients reported gastrointestinal disturbances; sedative effect was noted in some patients
Stefan, 1959[75]	46 menopausal women; 34 girls with juvenile menstrual disorders; 12 women with general menstrual disorders; 2 pregnant women	Isopropanolic extract (Remifemin tablets) or ethanolic extract (Remifemin solution)	No data on duration available	Adverse events were not observed
Stiehler, 1959[74]	18 menopausal women; and 53 girls with amenorrhea and juvenile menstrual disorders	Isopropanolic extract (Remifemin tablets) or ethanolic extract (Remifemin solution)	No data on duration available	Adverse events were not observed
Brücker, 1960[76]	517 women with dysmenorrhea and menopausal complaints	Isopropanolic extract (Remifemin tablets) or ethanolic extract (Remifemin solution)	No data on duration available	Adverse events were not observed
Heizer, 1960[77]	66 menopausal women; 23 hysterectomized or ovariectomized women; 21 young women with amenorrhea, oligomenorrhea, or dysmenorrhea	Isopropanolic extract (Remifemin tablets) or Ethanolic extract (Remifemin solution)	2–18 mo	Adverse events were not observed
Starfinger, 1960[78]	105 menopausal women	Ethanolic extract (Remifemin solution)	No data on duration available	Adverse events were not observed
Görlich, 1962[79]	235 women with hormone-related conditions, including amenorrhea, polymenorrhea, juvenile menstrual disorders, PMS, menopausal complaints, or pregnancy	Isopropanolic extract (Remifemin tablets) or Ethanolic extract (Remifemin solution)	Up to 1 y	Adverse events were not observed
Kesselkaul, 1957[80]	62 menopausal women	Ethanolic extract (Remifemin solution)	No data on duration available	Adverse events were not observed
Langfritz, 1962[81]	73 patients with juvenile menstrual disorders	Ethanolic extract (Remifemin solution)	3–12 mo	Adverse events were not observed
Schildge, 1964[82]	135 patients with PMS	Ethanolic extract (Remifemin solution)	3–6 mo	Adverse events were not observed
Daiber, 1983[25]	36 menopausal women	Ethanolic extract (Remifemin solution)	12-wk open study	No adverse events reported
Vorberg, 1984[26]	50 menopausal women	Ethanolic extract (Remifemin solution)	12-wk open study	4 mild gastrointestinal disturbances
Warnecke, 1985[27]	19 menopausal women	Ethanolic extract (Remifemin solution)	12-wk open study	No adverse events reported
Pethö, 1987[28]	50 menopausal women	Isopropanolic extract (Remifemin tablets)	24-wk open study	No adverse events reported
Stoll, 1987[29]	26 menopausal women	Isopropanolic extract (Remifemin tablets)	12-wk double-blind study	12 minor side effects reported 1 patient with varicosis developed thrombophebitis
Mielnik, 1996[85]	34 menopausal women	Not specified	24 wk	No side effects reported

TABLE 6. *Continued*

Jacobson et al, 2001[72]	85 breast cancer patients; 59 concurrently taking tamoxifen	Isopropanolic extract	8-wk randomized study	2 serious adverse events in the *Cimicifuga*/tamoxifen group; 6 minor adverse events in the *Cimicifugal*/tamoxifen group; 2 minor adverse events in the *Cimicifuga* group; no adverse events related to *Cimicifuga* treatment
Todorova, unpublished data (2001)	100 (23 with hysterectomy) menopausal women	Isopropanolic extract (Remifemin tablets)	12–52 wk	One report of exanthema facialis without irritation
Liske et al, 2002[31]	152 perimenopausal and postmenopausal women	Isopropanolic extract (Remifemin tablets)	24-wk controlled, randomized, double-parallel group study	5 gastrointestinal disturbances; 5 CNS adverse effects; 5 adverse effects on breasts and/or genitals; 4 nonspecified adverse events; all events were mild to moderate in severity

PMS, premenstrual syndrome; CNS, central nervous system.

group) were reported. Study investigators, however, concluded that none of the reported events were *Cimicifuga* treatment related. Similarly, two serious adverse events (both in the *Cimicifuga*/tamoxifen group) were reported but not deemed to be *Cimicifuga* related.

Dose-related safety

Although reports of adverse events associated with Remifemin and other *Cimicifuga* extract therapies have been few in clinical investigations, there have been reports of untoward reactions to large (unspecified) doses of *Cimicifuga*. These include hypotension, general relaxation, vertigo, tremors, headaches, giddiness, and occasional vomiting.[86] Many of these reported adverse reactions are from the early reports of *Cimicifuga* use dating back to the mid-19th century.[13] As such, it is unlikely that similar reactions occur with the appropriate use of the currently available, clinically tested *Cimicifuga* extracts. Although there are a number of *Cimicifuga* doses currently used without the occurrence of side effects, caution is warranted when administering any dietary supplements in quantities exceeding the recommended, clinically tested daily dose.

To confirm the safety of the commercially accepted doses of isopropanolic *Cimicifuga* extract, Liske and colleagues[31] conducted a 24-week controlled, randomized, double-blinded parallel-group study of two doses of the isopropanolic *Cimicifuga* preparation [Remifemin (standard dose: 39.0 mg/day; high dose: 127.3 mg/day)] in 152 perimenopausal and postmenopausal women. Both the standard- and high-dose groups reported "good" and "very good" tolerability ratings (standard: 94.7% at 12 weeks and 100% at 24 weeks; high: 82% at 12 weeks and 100% at 24 weeks), and adverse-event reports for both dose groups were comparable. The 19 reported adverse events were mild or moderate and can be classified as gastrointestinal effects (1 report in the standard-dose group; 4 reports in the high-dose group); central nervous system effects (1 report in the standard-dose group; 4 reports in the high-dose group); effects on the breasts or genitals (3 reports in the standard-dose group; 2 reports in the high-dose group); and other nonspecified effects (2 reports in the standard-dose group; 2 reports in the high-dose group). Whereas one patient reported metrorrhagia determined to be caused by an inactive endometrium, none of the adverse events reported in this study can be directly attributed to intake of the *Cimicifuga* extract.[31]

Safety in special populations

As HRT is contraindicated in women with estrogen-sensitive cancers of the breast and uterus, the possible tumor-promoting activity of alternative estrogen-like therapies requires special evaluation, particularly in relation to the clinical application of *Cimicifuga* extracts. Several clinical studies as well as human clinical trials (reviewed earlier in this section) have evaluated the potential of *Cimicifuga* extracts to induce proliferation of estrogen receptor–positive cells or changes in estrogen-dependent hormones (Table 7).

Estrogen naturally decreases during menopause, thus initiating an estrogen-dependent negative-feedback cycle that causes LH and FSH levels to increase.[87] Therefore, estrogenic activity would likely result in decreased levels of LH and FSH. A clinical trial of perimenopausal and postmenopausal women that investigated the effects of *Cimicifuga* on the female reproductive system over a 24-week period evaluated the physiologic effects of the medicinal herb based on vaginal cytology measures (degree of cell proliferation in the vaginal epithelium, the karyopyknotic index, and the eosinophilic index) and reproductive hormone lev-

TABLE 7. *Clinical studies highlighting Cimicifuga safety in special populations*

Reference	Study parameters	*Cimicifuga* formulation	Treatment duration	*Cimicifuga* effects on hormone levels	*Cimicifuga* effects on cell proliferation
Liske et al, 2002[31]	152 perimenopausal and postmenopausal women	Isopropanolic extract (Remifemin tablets)	24-wk controlled, randomized, double-parallel group study	No change in LH, FSH, prolactin, or sex hormone–binding globulin levels	No vaginal cell proliferation
Georgiev and Tordanova, 1997[88]	50 menopausal women	Isopropanolic extract	12 wk	Not reported	No change in endometrial thickness
Lehmann-Willenbrock and Riedel, 1998[30]	Hysterectomized women	Isopropanolic extract (Remifemin tablets)	24-wk study	No change in reproductive hormone levels	Not investigated
Nesselhut and Liske, 1999[53]	Postmenopausal women	Isopropanolic extract (Remifemin tablets)	12 wk	No change in hormone levels	No change in endometrial thickness
Jacobson et al, 2001[72]	85 breast cancer patients; 59 concurrently taking tamoxifen	Isopropanolic extract	8-wk randomized study	No change in LH and FSH levels	No regrowth of cancerous breast tissue
Maamari and Schreiber, 2001[84]	50 menopausal women, including 5 breast cancer survivors	Not specified	24-wk study	Not reported	No change in mammography, pap smear, and vaginal ultrasound
Düker et al, 1991[89,a]	52 menopausal women	Ethanolic extract	8-wk study	No reduction in FSH levels; significant reduction in LH levels	Not investigated

LH, luteinizing hormone; FSH, follicle-stimulating hormone.
[a]Data are contradictory of lack of estrogenic effect of *Cimicifuga.*

els.[31] The vaginal cytology measures demonstrated that *Cimicifuga* did not induce cell proliferation or other adverse effects nor cause significant alterations in E_2, LH, FSH, prolactin, and sex hormone-binding globulin levels after treatment with the standard (39.0 mg/day) or high (127.3 mg/day) dose of *Cimicifuga*. On the basis of vaginal cytology and hormone findings from this clinical study, it appears that the beneficial effects of *Cimicifuga* extracts on menopausal symptoms are not associated with systemic estrogen-agonistic effects. The noted lack of estrogenic effect of *Cimicifuga* on female reproductive hormones has also been demonstrated in a study of hysterectomized menopausal patients.[30]

The results of Liske et al[31] confirm data from Nesselhut and Liske[53] that support a lack of estrogenic effect of *Cimicifuga* on the female genital tract. In their study, postmenopausal women treated with an isopropanolic *Cimicifuga* extract (136 mg crude drug per day) for 3 months showed no change in the endometrial thickness, monitored by transvaginal sonography, or in hormone levels (E_2, LH, FSH, and prolactin). Similarly, Jacobson et al[72] found that *Cimicifuga* treatment did not significantly alter LH and FSH levels in breast cancer survivors as compared with placebo-treated breast cancer patients, nor did the extract induce cancerous regrowth of breast tissue. Likewise, a study of 50 women, including 5 breast cancer survivors, treated with 20 mg/day of a *Cimicifuga* extract for relief of hot flashes and night sweats found that mammography, pap smear, and vaginal ultrasound results were comparable to baseline over a 24-week period.[84] A similar study of 50 women treated with an isopropanolic *Cimicifuga* extract noted that endometrial thickness was not influenced by the 12-week treatment.[88] Although long-term studies are needed, these data suggest that *Cimicifuga* is safe for women who reject or cannot take HRT.[84]

In contradiction to reports demonstrating an estrogen-antagonistic or nonestrogenic effect of *Cimicifuga*, some findings have been consistent with an estrogenic mode of action. In an open study of 52 menopausal women treated with *Cimicifuga*, Düker et al[89] report that although FSH levels did not decrease in comparison to placebo-treated patients, the *Cimicifuga* extract significantly reduced LH levels in the treated population. The selective suppression of LH secretion in

menopausal women treated with *Cimicifuga* extracts in this study points toward an estrogenic mode of action corresponding with the natural decrease in estrogen, which triggers a feedback cycle causing an increase in LH levels. Similarly, an open, comparative study by Warnecke showed proliferation of the vaginal epithelium, which could be indicative of an estrogenic mechanism of action.[27] However, absence of some data, including baseline FSH and LH levels, placebo controls, and controls for effective randomization, may limit the interpretability of these studies.

DISCUSSION

Benefit-risk analysis

Uncontrolled reports, postmarketing surveillance, and human clinical trials including more than 2,800 patients demonstrate the low incidence of adverse events, particularly reports associated with single-agent *Cimicifuga* use. Likewise, scientific investigations of the estrogenic activity of isopropanolic extracts of *Cimicifuga* demonstrate the safety of this therapy for a period of 24 weeks in individuals with a history of estrogen-dependent neoplasms.

The largest postmarketing clinical investigation of Remifemin reports that more than 80% of the treated patients showed improvement in menopausal symptoms, including hot flashes, sweating, headaches, vertigo, palpitation, tinnitus, nervousness/irritability, and depression.[24] Similarly, controlled, randomized studies have found that an isopropanolic *Cimicifuga* extract (Remifemin Menopause) was just as effective as therapies using estrogen or the psychoactive drug diazepam for managing menopausal symptoms over a period of 3 months.[27,28,30] Although many of these studies have methodological flaws, including lack of a placebo-controlled arm, these data, coupled with the excellent safety record and extremely low incidence of adverse events, suggest a positive benefit-to-risk ratio.

CONCLUSIONS

Cimicifuga isopropanolic extract has a long history of clinical use and has been used in Europe for almost 50 years to manage menopausal symptoms. Supported by postmarketing experience, clinical trials, and toxicology reviews of up to 6 months in duration and by in vitro and in vivo studies, the favorable safety and toxicity profile of *Cimicifuga* extracts for use in women with hormonal disorders, including menopause, has been clearly demonstrated. It is noteworthy that the commercially available isopropanolic *Cimicifuga* formulation (Remifemin) has been widely studied and shown not to induce cytotoxic, mutagenic, carcinogenic, or teratogenic effects at doses much larger than the human therapeutic dose. Thus, *Cimicifuga* extracts, such as the isopropanolic formulation, appear to be safe for use in women currently experiencing menopausal symptoms.

Because of concerns regarding the safety of treatments used to relieve menopausal symptoms, particularly the potential adverse effects of HRT, the safety of alternative treatments requires intense examination. Although few reports suggest that *Cimicifuga* may act through an estrogen-like mechanism, there is significant scientific data stemming from various in vitro and in vivo studies that seriously cast doubt upon this hypothesis. Although we recognize that a large, long-term study using rigorous methodology is needed to estimate the size and mechanism of treatment effect, after reviewing all of the data regarding adverse events and toxicology, practitioners should be reassured that *Cimicifuga* treatment appears to be a safe option for women who wish to take it for relief of menopausal symptoms.

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