

REVIEW: Long-Term Efficacy and Safety of a Special Extract of *Rheum rhaponticum L.* (ERr 731[®]) in Reducing Hot Flashes and Other Menopausal Symptoms

Menopausal symptoms can start several years before menopause and last for 5 years (or more) afterwards and negatively impact daily living and well-being. To date, the most effective and reliable therapy for menopausal vasomotor symptoms (e.g., hot flashes, night sweats) is hormone therapy (HT). But many women are either hesitant to consider this option or are not candidates for HT due to the increased risk of hormone-related cancers and cardiovascular disease. Even in ideal circumstances, HT is still not recommended as a long-term therapy and is primarily indicated for the treatment of moderate to severe vasomotor symptoms. And natural therapies, such as black cohosh or phytoestrogens from soy or red clover, may offer a higher degree of safety but have shown a varying degree of clinical success and lack adequate scientific support that demonstrates a high degree of efficacy.

In Germany, where research on herbal relief for menopausal symptoms has been conducted and widely prescribed since the 1940s, clinicians have been recommending a purified and standardized extract of Siberian rhubarb (*Rheum rhaponticum L.*) known as ERr 731 since 1993. Clinical studies have demonstrated that 1 tablet (4 mg) daily of ERr 731 offers significantly effective relief vs. placebo for the 11 most common menopausal symptoms, including hot flashes. Subjects have reported symptom reduction that continues over 3, 6, 12, and 24 months to help improve quality of life through additional improvements in sleep quality and reduced anxiety and depression.

Unlike HT, ERr 731 does not contain any forms of estrogen or very potent activators of estrogen receptors and appears to be a safer option for longer use than HT, SSRIs/SNRIs, and select herbals that suggest limited, short-term use for symptoms that can last for years. Preliminary research suggests that ERr 731 may act as a selective estrogen receptor modulator, or SERM, for estrogen receptor β , which may help explain both its efficacy and safety profile—supported by toxicology and well-designed clinical studies lasting up to 2 years.

MENOPAUSE: A NATURAL TRANSITION, NOT A DISEASE

Menopause is a significant event in the lives of most women, as it marks an end to the ability to reproduce. Because this transition is a normal part of every woman's life, it therefore requires no "prevention" like other symptomatic complaints associated with a clinical condition. There are, however, ways to reduce or eliminate associated complaints that can seriously impact daily functioning and quality of life.¹⁻³ In 2005, the National Institutes of Health (NIH) issued a statement that identified a need for "demedicalization" of menopause to help promote the recognition of symptoms of this natural life transition, as well as increase awareness of

natural therapies to alleviate them.

Menopause is the clinical term used after menstruation has ceased for one year, after which women are considered *postmenopausal*. *Perimenopause* is used to describe the timeframe leading up to the final menstrual period, which is signaled by irregular menstrual bleeding, erratic hormone levels (e.g., estrogen, progesterone), and the onset of menopausal symptoms.^{4,5} In the last 1 to 2 years before the final menstrual period, estrogen loss accelerates and symptoms may become more pronounced. Perimenopause, typically starting after age 40, averages 5 years.^{3,6}

A woman's reproductive system begins aging at birth, but age itself is a poor indicator for the onset of *natural menopause* due to the wide age range at which it occurs.⁷ The age range for natural menopause is 40 to 58 years, with 51 being the median age for menopause in the Western world.^{3,7} This transition is also influenced by genetic and lifestyle factors, such as smoking and body mass index (BMI).^{3,6} An estimated 6,000 American women transition to menopause every day, with 75% of women aged 50 to 55 years old assumed to be postmenopausal.⁷

Induced menopause is the cessation of menstruation caused by suppression of ovarian function either through surgical removal (oophorectomy), pelvic radiation therapy, or chemotherapy.^{3,5,7-9} Women with induced menopause may suffer symptoms of a greater intensity or frequency. Over 90% of women who undergo bilateral oophorectomy suffer from hot flashes and other symptoms that can be severe and long-lasting.⁸

SYMPTOMS OF MENOPAUSE

Each woman experiences menopause in a unique way. The most common symptoms typically fall into 11 categories (**Table 1**), with hot flashes being the most common and potentially debilitating. Nearly 80% of women in Western countries suffer from hot flashes, with 30% reporting hot flashes severe and frequent enough to seriously affect quality of life.⁴ One study on vasomotor symptoms suggests highly symptomatic women may underreport the number of objectively measured hot flashes they experience by 43%.¹⁰

Hot flashes (also referred to as hot flashes) and associated symptoms impact daily functioning (work, social life) and sleep, as well as reported state of health.^{1-3,5} Research suggests that poor sleep quality, fatigue, and memory decline may be directly connected to the number and severity of daily hot flashes and loss of estrogen and progesterone. Sleep disturbances are the fourth most frequent menopausal complaint, with up to 40% to 60% of peri- and postmenopausal women reporting trouble sleeping.^{3,5,6} And more than 40% of peri- and postmenopausal women experience physical and mental exhaustion and cite forgetfulness as a menopausal symptom. Cognitive function, such as verbal memory performance and verbal fluency, has been shown by some research to be negatively impacted by both sleep disturbances and hot flashes in women with moderate to severe symptoms.¹⁰

Over 30% of peri- and postmenopausal women also suffer from vaginal dryness, which along with other symptoms contributes to loss of libido or sexual dysfunction.^{3,5,6} Unlike other menopausal symptoms that generally dissipate or disappear with time, it may continue indefinitely or lead to atrophic vaginitis, a risk that increases with use of aromatase inhibitors.⁸

Table 1. Top Menopausal Symptoms

The following 11 categories of symptoms are measured in the Menopause Rating Scale (MRS):¹

- Hot flushes and sweating
- Heart complaints
- Sleep disturbances
- Depressive mood
- Irritability
- Anxiety
- Physical and mental exhaustion
- Sexual problems
- Urinary tract complaints
- Vaginal dryness
- Joint and muscle complaints

Symptom prevalence varies greatly, which may also be influenced by menopausal stage.³

A CLOSER LOOK AT HOT FLUSHES

Not every woman will experience hot flushes, but most do at some point—with frequency and intensity varying greatly. Seventy-five percent of women over 50 years old report hot flushes, which can begin to affect women even in the premenopausal stage (14% to 51%). But they are most frequent in perimenopausal (35% to 50%) and postmenopausal (30% to 80%) women.⁵ Hot flushes are the primary reason women seek medical care for menopausal symptoms and also the primary reason they consider HT.^{1,3,5,8} An estimated 10% of women may experience hot flushes for 10 years or more.⁵

This climacteric symptom, lasting from 5 to 10 minutes, has been described as a wavelike feeling of intense warmth that rises suddenly in the chest, often spreading to the neck and face.^{1,3,11} Simultaneously, a woman may also experience increased anxiety, irritability, panic, sweating, heart palpitations, and flushing or reddened blotches of skin. This sensation may be followed by a chill.^{1,3,5,9,11}

While the physiology of this vasomotor response is unknown, it appears to be a result of dysfunction of thermoregulatory centers influenced by the hypothalamus.^{1,3,5,9,12,13} Furthermore, estrogen withdrawal, rather than low circulating estrogen, is postulated to be the genesis of hot flushes, which is reinforced by observations in women who suddenly discontinue HT.^{1,5,8,9,12} The hypothalamus is the body's master regulator, not only for body temperature but also blood pressure and electrolyte balance, energy metabolism and metabolic rate, reproduction and sleep cycle, and autonomic activity of the stress response (psychosocial and systemic). Declining estrogen causes a

decrease in endorphins in the hypothalamus, causing the hypothalamus to increase the release of the neurotransmitters norepinephrine and serotonin. This influences not only mood and cognitive function, but potentially lowers the set point of thermoregulatory unit, changing the core body temperature and triggering heat loss mechanisms to create the hot flush sensation. Norepinephrine is suggested to be the primary neurotransmitter influencing these thermoregulatory changes.^{1,9,13}

When ovarian follicles fail to secrete estrogen to provide negative feedback for regular cycling, pituitary gonadotropin increases and leads to increased levels of luteinizing hormone (LH).^{1,14} Though no causal relationship between the level of circulating LH and hot flushes has been demonstrated, hot flush occurrence has been correlated to pulses in LH levels.¹ These pulses may also influence the thermoregulatory unit by their effect on hypothalamic neurons.⁵

Hormonal fluctuations in progesterone, as well as estrogen, are another purported systemic influence for hot flushes.¹¹ A decline in progesterone, which exerts sedative and antiexcitatory activity by modulating GABA receptors, may also contribute to anxiety and altered sleep patterns.¹⁵

TREATMENTS FOR MENOPAUSAL SYMPTOMS

While almost 70% of perimenopausal women develop menopausal symptoms, many do not seek conventional medical care or report dissatisfaction with pharmaceutical recommendations.¹⁶ Surveys suggest that 80% of peri- and postmenopausal women have tried or currently use dietary supplements, fueled not only by personal beliefs but also by warnings about HT from the Women's Health Initiative (WHI) and the North American Menopause Society (NAMS).^{3,12,16,17}

A discussion of the effectiveness of any treatment of menopausal symptoms must be prefaced with an explanation of the difficulty in achieving sound quality research in this area, which is frustrating not only for women in transition but also their healthcare providers and leading health authorities. Methodological challenges are a common thread in clinical trials for hot flushes—for any type of therapy—for a number of reasons, including:

- *The placebo effect.* Many menopausal studies do not include a placebo arm. When they do, dropout rates are high in placebo groups due to lack of effect, which contributes to a larger placebo effect in those that remain. This makes it difficult to discern if no treatment whatsoever would have been just as effective.^{1,8,9,11,13,18} Menopause trials for pharmaceutical and botanical therapies report a strong placebo effectiveness rate for hot flushes.^{1,9,11,18,19} A substantial placebo effect also exists for behavioral therapy trials.⁹
- *Study population.* Most studies fail to adjust or stratify for age or transitional stage.^{3,11} Or adequately screen for pre-existing or current disorders (physical and psychological), which also influence symptomatology. The overlap of poor health with the decline in estrogen and progesterone may make it difficult to evaluate treatment success. Previous use of HT or current use of other menopausal treatments or drugs for other conditions may also affect results. Tamoxifen, for example, may increase hot flushes.^{1,13}

- *The nature of menopause.* Not all women suffer symptoms equally, and studies may not stratify according to symptom severity.^{3,11} A closer look at trials that show a significant percentage in improvement often reveal only a modest decrease in the actual number of hot flashes. This may be due to the fact that many studies are conducted with postmenopausal women. Menopausal symptoms for many women decrease over time, contributing to placebo effect in clinical trials.^{8,11,18} Complaints during the menopausal transition are also difficult to distinguish from signs of aging.³
- *Limited resources, duration, and quality control.* There is a current lack of standardization for outcome measures and patient monitoring, and most trials are only 4 to 6 weeks.¹¹ Without blinding, studies may also reflect investigator bias.^{4,6} Natural approaches are also much less likely to be the subject of clinical studies, which are often conducted with a limited budget and lack resources for quality control. And herbal preparations can vary widely in quality and active ingredient content depending on manufacture.^{3,11,12,16,17} While the Commission E in Germany has closely evaluated the safety of botanicals and dietary supplements for over 20 years, safety measures in other countries (e.g., Asia) may not be so stringent.¹⁷ Variations in natural delivery methods (e.g., soy flour vs. soy isoflavone extracts) and dosing may also influence results.^{3,11} This makes comparisons between studies claiming to use the same ingredient difficult.¹¹

Experts agree that well-controlled trials are needed for both pharmaceutical and nonpharmaceutical approaches, and that adequate efficacy and safety data are lacking.^{5,8,9}

PHARMACOLOGICAL TREATMENTS FOR VASOMOTOR SYMPTOMS: DEMONSTRATED RELIEF, BUT WITH RISK

Hormone therapies for relief of menopausal symptoms offer more predictable relief, but are not without risks. Women turn to HT—estrogen or progesterone alone or in combination—most often due to hot flashes, which can be reduced in frequency by 70% to 80% with HT.^{1,3,12,19} Despite its benefits, which include osteoprotection, HT is currently recommended only for moderate to severe vasomotor symptoms due to potential increased risk of breast cancer and cardiovascular events and other unwanted effects, such as atypical bleeding and endometrial hypertrophy, nausea and vomiting, altered mood, breast tenderness, headache, weight change, dizziness, venous thromboembolic events, rash and pruritus, cholecystitis, and liver effects.^{3,5} Women over 60 years old who experienced natural menopause at a typical age and never used HT are discouraged from doing so without compelling reasons.⁵

Mood modulators (antidepressants), gabapentin (anticonvulsant), and clonidine (antihypertensive) are commonly recommended for short-term use in highly symptomatic women who are not HT candidates, though these drugs have not been approved by the FDA for relief of vasomotor symptoms.^{3,5,20} Selective serotonin re-uptake inhibitors (SSRIs) and selective nor-epinephrine reuptake inhibitors (SNRIs), which may cause headache, nausea, anxiety, and insomnia, can also complicate sexual dysfunction.^{3,8} Discontinuation symptoms are also common.⁸ The mechanism of action in these approaches for hot flush relief is unclear, but it appears to be

independent from that which affects mood.^{3,12,13,20} Clonidine and gabapentin have similar potential adverse effects.^{3,9,13} Research on these pharmacological alternatives to HT suggest they are “not optimal choices for most women” due to a lack of supported data on safety and efficacy, which is generally less than HT but superior to placebo.^{1,5,8,13,20} There are no trials that directly compare efficacy of mood modulators or gabapentin to HT, and optimal duration of treatment is unknown.^{8,20}

NATURAL APPROACHES FOR HOT FLUSH REDUCTION: SAFER BUT LESS RELIABLE RELIEF

For less symptomatic women or those contraindicated or unwilling to consider HT, national health organizations suggest natural therapies based on existing safety data for short-term use. These nonhormonal therapies, however, have shown only modest efficacy in clinical studies (attributable to clinical trial design), with little data on the effects on other symptoms or long-term use.^{3,8,9,16,21} While clinical experience suggests a degree of reliability for popular natural approaches, a lack of supporting evidence and concerns about manufacturing safety, drug interactions, and potential estrogen mimicking effects may discourage widespread clinical use.¹⁶

Natural approaches for hot flush relief generally fall into 3 categories—phytoestrogens, nonphytoestrogens, or mixtures of both—which aim to reduce the daily vasomotor symptoms (frequency, intensity, and number) and improve quality of life.^{3,11,12,16,17,22-25} Based on empirical observation by physicians worldwide, all of these approaches offer women relief for a wide variety of menopausal symptoms.²¹

Phytoestrogens reflect the largest increase in botanical and dietary supplements in the U.S., and the patients who use them are the fastest growing population segment.^{12,16} This class includes soy, red clover, flax, hops, hesperidin, and kudzu extracts. These products contain specific active compounds that possess gentle estrogen mimicry that are much less potent than HT.^{3,16,26,27} Unlike HT, however, they also demonstrate a variety of SERM activity—agonistic or antagonistic—to influence the body in different ways. Research suggests that approaches that selectively target specific estrogen receptors offer more selective clinical benefits, as opposed to global effects caused by HT.²⁸

The nonphytoestrogen class includes the well-known botanical black cohosh (once thought to display estrogenic activity), essential fatty acids, vitamin E, and newcomers such as succinate-based compounds.^{9,16,18,22,25,29,30} Phytoestrogen blends approach menopause physiology and biochemistry from a multidimensional perspective and represents classic clinical empiricism (i.e., less scientific support).¹⁶ Frequently, traditional Chinese and Ayurvedic botanical products fall into this classification system. Assumed synergy between ingredients underlies the formula profile.

In regards to hot flush reduction, recent meta-analyses of well-designed randomized controlled trials (RCTs) on a variety of soy, red clover, flax, hops, and black cohosh preparations reveal inconclusive results or demonstrate a weak impact on vasomotor symptoms when compared to placebo and prescription hormone and nonhormone therapies. Reviews of red clover and soy preparations suggest an average reduction of 1.5 hot flashes

per day, regardless of the form used.^{3,11,12} RCTs on flax lignans and select prenylflavonoids from female hop cones demonstrate no statistically significant benefit in reducing hot flush incidence.¹¹ To date, black cohosh used in isolation or as part of a multibotanical regimen shows little potential as an important therapy for vasomotor symptom relief vs. placebo.^{11,21-25}

Understanding the real efficacy of currently available products requires higher quality research, and the search for natural products that more effectively manage vasomotor symptoms continues. In the final analysis, most reviewers share similar views. First, definitive conclusions are difficult given the wide variation in product composition and dose. Secondly, there is a general agreement in comprehensive reviews that most phytoestrogen therapies (e.g., soy/red clover isoflavones, flax lignans) and black cohosh offer negligible effectiveness vs. placebo in reducing the severity and frequency of hot flushes. But most importantly, there appears to be little evidence of harm with short-term use of 3 months to 2 years for most natural-based therapies.^{11,13,15,18,23,24}

ERr 731 REPRESENTS A NEW ERA OF PHYTOESTROGEN RESEARCH FOR MENOPAUSAL HOT FLUSH RELIEF

From the roots of Siberian rhubarb (*Rheum rhaponticum* L., family Polygonaceae), comes a special phytoestrogen extract for menopausal complaints known in scientific literature as ERr 731.^{4,14,31-39} This garden rhubarb species is similar to the well-known vegetable rhubarb (*R. rhubarbarum*) but different from the medicinal rhubarbs used in traditional medicine as stronger laxatives—Chinese rhubarb (*R. palmatum*) or Indian rhubarb (*R. officianale*)—that must be used with caution.^{38,40} These medicinal rhubarbs contain a smaller amount of beneficial tannins and a larger amount of anthraquinones (e.g., emodin, rhein) that not only have a laxative effect but may also increase the risk of unwanted side effects in the breast and endometrium due to their potent activation of estrogen receptor α (ER α).^{4,33,38} Conversely, Siberian rhubarb, also known as rhapontic rhubarb, contains few anthraquinones near the root and a larger amount of hydroxystilbene compounds. And ERr 731 does not demonstrate either a laxative effect or potent ER α activity.^{33,38}

The main active constituent of ERr 731 is the glycode rhaponticin, followed by desoxyrhaponticin. The aglycones (metabolites) rhapontigenin and desoxyrhapontigenin are present in a lesser amount—about 5% of the extract.^{32,34,35,38} In plants, these secondary metabolites are synthesized to protect against viral and microbial attack, disease, and ultraviolet exposure.⁴¹ It is not yet clear, however, which compound(s) are responsible for observed clinical benefits.^{31,34} These hydroxystilbene compounds are structurally related to resveratrol—another phytoestrogen with demonstrated SERM activity—from which they are derived.^{16,18,35,38} Natural stilbene compounds, such as resveratrol and its derivatives, have shown great therapeutic promise because of their low toxicity and demonstrated activities against inflammation and cancer.^{34,36} Rhaponticin and rhapontigenin, for example, have been used for years in Asia for their antithrombotic and antiallergenic effects.⁴²⁻⁴⁵

The mechanism of action of ERr 731 is still not completely understood, but is the subject of current in vitro and in vivo research.^{4,14,32,33,36} Like many botanicals, this extract contains multiple active compounds that may work

synergistically to relieve a broad range of menopausal symptoms. ERr 731 contains no estrogen and meets the commonly accepted defining criteria for SERMs via its estrogen receptor selectivity on estrogen receptor β (ER β) and tissue selectivity.^{4,16,35,38} (Estrogens regulate gene expression by binding to ER α and ER β , influencing production of cytokines and neurotransmitters and other biological functions.) The total ERr 731 extract, as well as its individual compounds, have been demonstrated to act as potent, selective ER β agonists in human endometrial cells, without affecting ER β -mediated activities.³⁴

Neurotransmitter Modulation. Activation of ER β , which mediates the anxiolytic and antidepressant effects of estrogen, has been suggested to alleviate menopausal symptoms, including depression and anxiety.^{32,46} Some research suggests that ER β negatively regulates ER α , and may therefore protect against ER α -mediated effects in the breast and endometrium.^{31,33} This targeted influence on ER β may explain why clinical evidence demonstrates the effectiveness of ERr 731 in relieving menopausal symptoms—specifically hot flushes, poor mood, and anxiety.^{14,31,32} The similarity of menopausal and anxiety symptoms have been demonstrated in published literature, and both are more pronounced in perimenopausal women than postmenopausal women. It has even been suggested that anxiety symptoms precede hot flushes, and higher anxiety scores show a correlation to a greater incidence of hot flushes in clinical observations.³²

In addition to ER β specificity, ERr 731 constituents rhapontigenin and desoxyrhapontigenin have demonstrated inhibition of monoamine oxidase A (MAO) with serotonin as a substrate.^{32,36,47} Though these specific constituents together comprise less than 5% of the extract, it has been suggested that digestion may produce large amounts of these aglycones via deglycosylation of rhaponticin and desoxyrhaponticin by intestinal bacteria.^{34,43,44} Research also suggests that rhapontigenin is the active molecule of rhaponticin.^{41,42} This particular mechanism of action has been suggested to favorably modulate serotonin and catecholamine metabolism to support a healthy mood and cognitive function.^{32,46}

ERr 731 may therefore enhance neurotransmitter levels to offer menopausal symptom relief in a manner similar to mood modulators, which also have an unknown mechanism of action for hot flush relief.³⁶ While further study is needed, improvement in subjective measures in short- and long-term clinical studies appear to support this hypothesis.

Luteinizing Hormone Stabilization. At the end of the 108-week clinical study and observational studies with ERr 731, LH levels did not noticeably increase, whereas FSH increased as expected (as measured at the end of 96 weeks). These findings suggest that ERr 731 may help stabilize LH. A working hypothesis for this potential mechanism of action is that ERr 731 may favorably modulate gonadotropin-induced secretion of LH, as demonstrated in experimental studies with a natural compound structurally similar to resveratrol and ERr 731 constituents.¹⁴ Further study, however, is needed.

Antioxidant Activity. Phytochemical studies of stilbene derivatives—including rhaponticin, desoxyrhaponticin, rhapontigenin, and desoxyrhapontigenin—have demonstrated protection against oxidative damage by modulating cellular signaling pathways and inhibiting lipoxigenase.^{48,49} Oxidative stress

contributes to menopause and age-related physiological decline, and some research suggests that supporting the body's antioxidant defense may be of particular benefit during and after the menopausal transition—especially for those who cannot take HT or do not follow a healthy diet.^{50,51} The root of *Rheum rhaponticum* naturally contains significant amounts of the antioxidant flavonoid quercetin.⁵² ERr 731 has not been specifically studied for antioxidant activity.

ERr 731 RESEARCH: EXTENSIVE AND WELL-DESIGNED

Research to date suggests that ERr 731 may be the first phytoestrogen extract to transcend the placebo effect in menopausal clinical studies to offer a higher degree of effectiveness with minimal safety concerns for long-term use.

In Vitro Studies. *In vitro* studies with ERr 731 and its constituents demonstrate tissue-specific binding and activation of ER β in various cell lines (e.g., endometrial, bone) that is comparable to HT. Conversely, neither ERr 731 nor its aglycones rhapontigenin and desoxyrhapontigenin influenced ER α activity in human endometrial cells that naturally express ER α .³¹⁻³⁵ In human bone cells, where ER α activity is favorable, ERr 731 demonstrated only weak but sustained agonistic effects on ER α .³¹

In Vivo Studies: Toxicity. Artificial stilbene compounds, such as tamoxifen and raloxifene, carry an increased risk of uterine cancer. HT, which demonstrates a higher affinity to ER α , and even large long-term doses of soy have also shown hypoproliferative effects in the uterus. Single- and repeat-dose toxicity studies have been conducted *in vivo* with ERr 731. These long-term studies were required by German regulatory authorities to confirm a lack of toxic effect on organs and tissues.^{37,39}

Two *in vivo* animal studies (4 weeks and 13 weeks) were conducted with ERr 731 doses from 100 mg to 1,000 mg per kg of body weight per day (mg/kg bw/day). The no adverse effect level (NOAEL), determined to be 1,000 mg/kg bw/day, is ~14,000 times greater than the recommended dose of 4 mg daily. In a woman weighing 60 kg (~132 lb), that equates to ~0.07 mg/kg bw/day. The studies demonstrated no significant effects in clinical observations (except for fecal appearance at highest doses, suggesting incomplete absorption), body weight, ophthalmic observations, electrocardiograms, hematology parameters (except in 13-week study where a decrease in glucose levels was seen at 1,000 mg/kg bw), clinical biochemistry parameters, urinalysis parameters, organ weights (including uterine weight), or macro- or microscopic findings (even in genital tracts). A subsequent repeat-dose *in vivo* toxicity study was performed for 4 weeks and showed results similar to the toxicity studies detailed above, confirming the predicted safety of ERr 731.^{37,39}

In vivo mutagenicity studies also suggest predicted safety. In a preliminary uterotrophic assay, neither ERr 731 nor its major constituent rhaponticin demonstrated any detectable signs of uterotrophy after a single dose.^{31,33} Additional genotoxicity studies for mutagenic potential—including the Ames test, cell mutation assay at thymidine kinase locus of L5178Y cells, micronucleus test for bone marrow cytotoxicity, and immunotoxicity analysis of leukocytes—also showed no relevant variations with ERr 731.

In Vivo Studies: Metabolism. In a preliminary study, blood samples were taken at 1, 2, 3, 4, 5, 6, and 24 hours in a female subject. Rhaponticin was detectable between 1 and 5 hours (maximum level ~3 pg/ml after 3 hours), suggesting stability before deglycosylation and rapid metabolism. Its aglycone rhapontigenin was never detected, which is in agreement with other research suggesting that the detectable plasma half-life of rhapontigenin is relatively short.⁵³ (Plasma samples from separate *in vivo* toxicity studies showed similar results for both rhaponticin and rhapontigenin, as well as a corresponding pattern for desoxyrhaponticin and its aglycone desoxyrhapontigenin.)^{37,39}

Clinical Studies. Well-designed clinical studies (**Table 2**) also suggest an excellent safety profile for ERr 731, which has been well-tolerated in observational studies up to 2 years:^{4,14,32,38}

- 12-week multicenter, prospective, randomized, double-blind, placebo-controlled, type III, phase IV clinical study (Clinical Study #1)
- Long-term efficacy evaluation in 1- and 2-year open observational studies (Clinical Study #2)
- 6-month prospective post-marketing surveillance study in 70 gynecological centers (Clinical Study #3)
- Multicenter, prospective, randomized, double-blind, placebo-controlled, phase III clinical study (Clinical Study #4)

No adverse events have been associated with intake, and no clinically relevant changes in endometrial biopsies, bleeding, weight, blood pressure, pulse, or other standard laboratory parameters have been observed in these studies with over 400 patients.^{4,14,32,38} A lack of observed increases in progesterone and 17 β -estradiol also suggest safety for breast and endometrial tissue.¹⁴ Researchers suggest ERr 731 to be “highly effective” vs. placebo in relieving climacteric and anxiety-related menopausal symptoms. Anecdotal reports from prescribing practitioners also support effective reduction of menopausal symptoms in patients.^{32,33}

ERr 731 CLINICAL STUDY HIGHLIGHTS

Clinical Study #1. 109 symptomatic perimenopausal women received either ERr 731 (n = 54) or placebo (n = 55) for 12 weeks. The ERr 731 group showed significant improvements in 11 common menopausal complaints. At 4 weeks, there was a significant decrease in the number and severity of hot flashes compared to the placebo group (p < 0.0001), along with a significant decrease in Hamilton Anxiety Scale (HAMA)^{††} total score (**Figure 1**) for somatic and psychic anxiety (p < 0.0001), and a general improvement in total Women's Health Questionnaire (WHQ)^{†††} score, which includes subscales for anxiety and poor mood. At 12 weeks, the ERr 731 group demonstrated a significant decrease in total Menopause Rating Scale II (MRS II)[†] score (p < 0.0001), as well as significant decreases in all 11 individual symptom scores compared to placebo (p < 0.0001). The treatment group showed significant improvements in HAMA scores (p < 0.0001) and on all subscale scores—vasomotor, psychosocial, physical, and sexual—on the Menopause-Specific Quality of Life (MENQOL)[†] assessment (p < 0.05). Further improvement in total WHQ \ddagger score (including improvement in 8 of 9 subscales) was also seen in ERr 731 subjects vs. a decline in total score for placebo subjects.^{4,32}

Table 2. ERr 731 Clinical Study Exclusion Criteria

Clinical studies for ERr 731 have been well designed to minimize factors such as major vasomotor triggers and pre-existing conditions that may influence outcomes. For example, exclusion criteria for the first clinical study included (among other criteria):⁴

- Regular cycles in prior 3 months
- Mandatory indication of HT
- PAP smear of class III/IV or endometrial hyperplasia
- Known or suspected sensitivity to ERr 731 compounds
- Concomitant use of approach for climacteric complaints, or use of a climacteric approach 3 months prior (6 months for HT)
- Medications that might impair results: corticosteroids, anti-hypertensives, psychoactive drugs (including sedatives), laxatives
- BMI < 18 or > 30 or abnormal eating habits (e.g., vegetarian, bulimia)
- Previous or existing thromboembolic disease or insufficiently controlled hypertension
- Type 2 diabetes; liver, kidney, or fat metabolism disorders; immunosuppression; malignant tumors
- Previous or existing psychiatric disorders (including depression)
- Smoking or suspected drug abuse
- Intake of alcohol intake \geq 10 mL ethanol/day or caffeine (e.g., chocolate, coffee) \geq 500 mg/day

Unlike many studies that include a broad spectrum of menopausal stages, this study was limited to perimenopausal women with active symptomatology who were in good health and following a reasonably healthy lifestyle pattern, which is critical to the success of any menopausal therapy.

Clinical Study #2. In this 108-week study, 80 subjects from the 12-week study above were followed for observational studies (OS I and II), along with a placebo group for OS I. In OS I (48 weeks), subjects received either ERr 731 (n = 39) or placebo (n = 41). In OS II (48 weeks), 51 women were given ERr 731 (23 subjects from the ERr 731 group and 28 women from the placebo group in OS I). ERr 731 demonstrated a further decrease or sustained alleviation of menopausal symptoms at 60 and 108 weeks (Figure 2). At 108 weeks, all subjects (now all receiving ERr 731, but with varying lengths of treatment) had an average of less than 1.4 slight hot flushes per day.¹⁴

Clinical Study #3. In this open observational study, 252 peri- and postmenopausal women enrolled at 70 gynecological practices were given ERr 731 daily at varied doses for 6 months. During the first 3 months, 243 of the participants took 1 tablet daily, 13 took 2 tablets daily, and 1 woman took 4 tablets daily. Over the course of the entire 6-month study, 228 women took 1 tablet daily and 6 took 2 tablets daily as recommended. For the majority of women, 1 tablet daily was enough to significantly relieve menopausal symptoms. Subjects showed a significant decrease in MRS⁺ total score, from an average of 14.5 points at baseline to 6.5 points ($p < 0.0001$) and reported a notable improvement in health-related quality of life.³⁸

Clinical Study #4. For 12 weeks, 112 symptomatic perimenopausal women were given one tablet daily of ERr 731 (n = 56) or placebo (n = 56) daily. At 12 weeks, ERr 731 subjects showed a significant reduction in the number of hot flushes, from a median of 12 to 2 (Figure 3). Based on the Hot-Flush-Weekly-Weighted-Score (HFWWS), this decrease in hot flushes with ERr 731 is comparable to those reported for an ultralow dose of HT. Furthermore, those with more severe hot flushes received the greatest benefit from the intervention. The treatment arm also demonstrated a significant reduction of the MRS total score, from an average of 27 points at baseline to 12.4, compared to a placebo-induced decrease from 27 to 24 points ($p < 0.0001$). ERr 731 subjects also showed significant reductions in each of the 11 individual MRS scores ($p < 0.001$ for vaginal dryness and $p < 0.0001$ for 10 other symptoms).³³

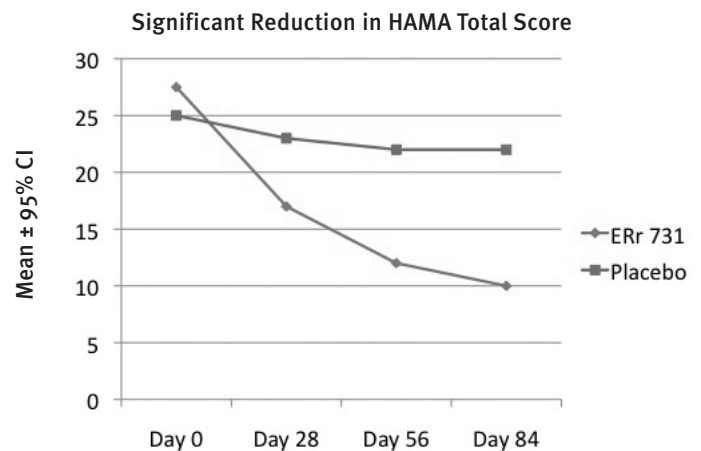


Figure 1. Results of Hamilton Anxiety Scale (HAMA) total score assessed by the investigator every 4 weeks, using a rating scale ranging from 0 (not present) to 4 (severe). At 28 days, the ERr 731 arm reported a noteworthy reduction in anxiety symptoms, with more subjects reporting “not present” to “mild” complaints, compared to baseline. In contrast, reported symptoms by the placebo arm remain mostly unchanged.³²

83% Reduction of MRS II Symptoms Maintained with Long-Term Use of ERr 731

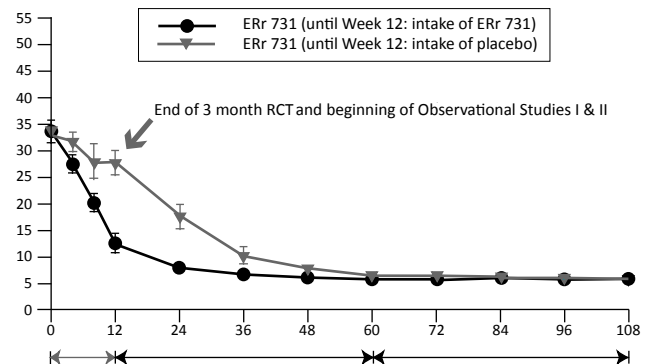


Figure 2. At 12 weeks, the ERr 731 arm showed a dramatic and statistically significant improvement in MRS II scores compared to placebo. At the end of 60 weeks, the original ERr 731 arm reported a slightly greater reduction in menopause symptoms vs. the original placebo group that began ERr 731 supplementation after 12 weeks. At the end of the second observational period (108 weeks), the original ERr 731 group had maintained a reduction in scores, which were comparable to end scores for the original placebo group.¹⁴

Comparison of Other Hot Flush Therapies

Approach	Effectiveness for Hot Flushes	Placebo Effect
Hormone Therapies (e.g., oral estrogen, combined estrogen and progesterone)	Consistent	Strong
	75% average ¹⁹ Range of 70% to 80% ¹²	58% average ¹⁹ Range of 41% to 61% ¹⁹
Phytoestrogens (e.g., soy/red clover isoflavones, flax lignans)	Varies Widely	Strong ^{11,56}
	Typically negligible vs. placebo in reviews ^{11,56} Up to 45% effectiveness rates have been cited ¹²	Range of 1% to 59% ¹¹

Table 3. For comparison purposes, data extrapolated from reviews of placebo-controlled studies of varying lengths.^{11,12,19,56}

Significant Decrease in Daily Hot Flushes with ERr 731

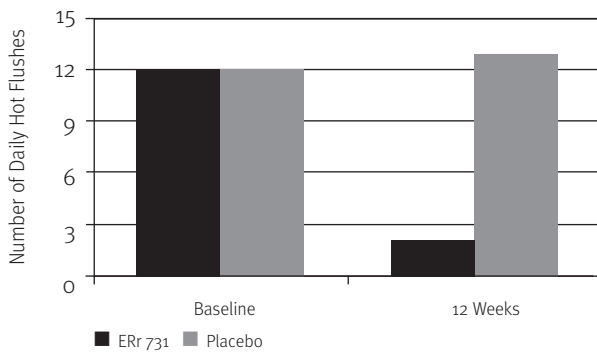


Figure 3. At 12 weeks, ERr 731 subjects reported a significant decrease in the median number of daily hot flushes vs. placebo.³³

POSTMARKETING SURVEILLANCE AND CONSUMER COMPLAINTS DATA

ERr 731[®] was commercially registered in Germany in 1993 and marketed as an alternative for women considering a nonhormonal approach to managing menopausal symptoms. In Germany, the marketing authorization holders (MAHs) of medicinal products such as ERr 731[®] are obliged to regularly submit postmarketing safety reports to regulatory authority.

The post-marketing surveillance data collected by the MAHs from 1993 (when the AE report collection began) to June 2014 have been published in *Integrative Medicine: A Clinician's Journal (IMC)*.⁵⁴

During this period, approximately 140 million daily doses of ERr 731[®] were placed on the German market, and 124 suspected AE reports were recorded. **On average, less than 1 suspected AE was reported for every million doses of ERr 731[®] sold.**⁵⁴ The most common of those AEs were hypersensitivity and gastrointestinal symptoms.

ERr 731[®] was introduced as a dietary supplement in 2009 in the U.S., in 2011 in South Africa, and in 2012 in Canada. In these countries, when a healthcare professional or consumer reports suspected AEs to Metagenics, the company is required to send the AE report to regulatory authorities (e.g., FDA). The secondary objective of the *IMC* article was to assess consumers' complaints in these regions from the date of the extract's launch to June 2014.

LIFESTYLE HABITS CRITICAL FOR SUCCESS OF MENOPAUSAL THERAPIES

The healthier a woman is when entering the menopause phase of her life, the easier the transition. The premenopausal stage is characterized by childbirth, parenting, family, and work obligations in which a woman may have been living an unhealthy or hectic lifestyle. Therefore, she may enter this period of hormonal and social change unfit or overstressed. How a woman experiences menopause is often seen as an opportunity for her to take care of herself for the first time in a long time.

During this period, approximately 13 million tablets had been sold in North America, and 79 complaints related to consumption of ERr 731[®] had been recorded. **On average, 6 consumer complaints were reported for every million doses of the extract provided to women.**⁵⁴ The main complaints were gastrointestinal symptoms and issues with the product not working as suggested. In South Africa, 120,000 tablets had been sold, and no consumer complaints had been recorded.

Postmarketing surveillance captures safety information that is more diverse than that generated from a clinical trial, which tests a relatively small group of selected participants in a more controlled environment for a fixed duration. The *IMC* article provides the picture of the safety profile of ERr 731[®] when it is used by thousands of consumers in real-life situations.

The study found that the incidence of AEs or consumer complaints can be considered to be very low, and therefore the extract is safe for most users. However, postmarketing surveillance has a well-known limitation of underreporting (i.e., not all consumers and clinicians reported the AEs). Therefore, the data should be interpreted with good judgment.

JAMA SYSTEMATIC REVIEW AND META-ANALYSIS

In a review article published in the Journal of American Medical Association (JAMA), researchers investigated the association between a broad range of plant-based therapies and improvements in menopausal symptoms based on published randomized clinical trials.

One of the therapies analyzed in this article was the use of ERr 731®.

The researchers found that ERr 731® was associated with the reduction of hot flashes.⁵⁵

The authors recognized the value of plant-based therapies for women seeking nonpharmacological approaches to managing menopausal symptoms. However, they also indicated that not all plant-based therapies worked, and several trials in their analysis had suboptimal quality. Future research with trials with more rigorous design is needed.

The JAMA article analyzed clinical trials of ERr 731® and confirmed its effect in reducing hot flashes. This efficacy information complements the postmarketing safety information published in IMCJ.

EFFICACY COMPARISON OF OTHER TREATMENTS FOR HOT FLUSH RELIEF

For a topline view of the relative effectiveness of HT and other phytoestrogen approaches, data have been extrapolated from reviews of placebo-controlled studies and presented in **Table 3** to facilitate discussion for clinical practice and implementation.^{11,12,19,56} As mentioned earlier, there is a lack of consistency in menopausal study design, including study duration, outcome measures subject criteria (e.g., transitional stage, symptom severity). For example, the HT studies reviewed were conducted with postmenopausal women or perimenopausal women who had ceased menstruation for 12 months or more, where hot flashes are typically less frequent and severe than in early perimenopause. The degree of effectiveness, therefore, is typically measured against a lower baseline value than in the ERr 731 clinical studies with perimenopausal women with more active symptomatology.

Due to careful study design, the placebo effect has been minimized in studies with ERr 731, which compares in efficacy to HT studies (where a larger average placebo effect has been observed). Though there is a current deficiency in well-designed studies of other phytoestrogen therapies, reviews of placebo-controlled trials demonstrate a strong placebo effect similar to HT studies. This potentially invalidates results seen with phytoestrogen approaches and effectiveness is therefore typically described as non-significant vs. placebo, although individual studies have shown favorable results.

All recommended therapies for menopause (hormonal or nonhormonal) are centered around lifestyle changes for more positive outcomes.^{5,8,9,21} Lifestyle factors not only influence the rate of transition, but also the degree of symptomatology. For example, a higher BMI is associated with more severe hot flashes, which can also be triggered by caffeine, alcohol, drugs, and spicy foods. Conversely, exercise, a healthy sex life, and relaxation breathing techniques can reduce symptomatology. This also explains why other nonpharmacological approaches to menopausal symptom relief—including stress management, behavioral therapy, chiropractic, and massage therapy—have been suggested to offer relief for some menopausal women.^{5,8,9,12,13}

CONCLUSION

ERr 731 is perhaps the most thoroughly tested phytoestrogen SERM to date that offers a more natural approach to relieving menopausal symptoms, including hot flashes. Published toxicology and clinical studies suggest reliable efficacy and predicted long-term safety with no associated serious adverse events reported to date. Furthermore, based on clinical results and experience, this novel extract may provide a greater benefit to those with more severe hot flashes.

ERr 731, used in conjunction with a patient-centered approach to menopausal relief, may therefore offer positive clinical outcomes for women in various stages of menopausal transition.

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[†] The Menopause Rating Scale (MRS) is a verbal questionnaire for subjectively measuring 11 common menopausal symptoms, including hot flushes, heart complaints, sleep problems, poor mood, irritability, anxiety, physical and mental exhaustion, sexual problems, bladder problems, vaginal dryness, and joint and muscular discomfort. MRS II includes the same subscales but is reformatted for self-administration. A score of 18 or more indicates moderate to severe symptoms.

^{††} The Hamilton Anxiety Scale (HAMA) is an interview rating scale to quantify 14 anxiety symptoms categorized as somatic (muscular, sensory, respiratory, gastrointestinal, genitourinary, and autonomic) or psychic (anxious mood, tension, fears, sleep disturbances, poor mood, and behavior at interview). Scores range from 0 to 56, with a higher score suggesting a greater degree of anxiety.

^{†††} The Women's Health Questionnaire (WHQ) is a 36-item questionnaire and diary to assess 9 areas of middle-aged women's physical and emotional health, including poor mood, somatic symptoms, anxiety/fears, vasomotor symptoms, sleep problems, sexual behavior, menstrual symptoms, memory/concentration, and feeling of attractiveness.

^{††††} The Menopause-Specific Quality of Life assessment (MENQOL) is a self-administered, 29-item questionnaire to determine differences in quality of life (including health status) between menopausal women and to measure changes in their quality of life over time.

