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ORIGINAL RESEARCH

First Time Proof of Sage's Tolerability and Efficacy in Menopausal Women with Hot Flushes

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ABSTRACT

Background: This trial aimed to assess the tolerability and efficacy of a fresh sage preparation in treating hot flushes and other menopausal complaints. Sage *(Salvia officinalis)* has been traditionally used to treat sweating and menopausal hot flushes, as well as to alleviate associated menopausal symptoms and as a general tonic. However, no clinical studies substantiating the use of sage in menopause have been published previously. ***Methods:*** In an open, multicenter clinical trial conducted in eight practices in Switzerland, 71 patients (intent-to-treat population [ITT], n=69; with a mean age of 56.4±4.7 years, menopausal for at least 12 months, and with at least five flushes daily) were recruited and treated with a once-daily tablet of fresh sage leaves for 8 weeks after an introductory baseline week. Parameters for the evaluation of efficacy were the change in intensity and frequency of hot flushes, and total score of the mean number of intensity-rated hot flushes (TSIRHF) as determined by diary protocol over the 2-month treatment period. Other variables included assessment of the Menopause Rating Scale (MRS) by the treating physician at baseline and after 2 months of therapy. ***Results:*** In the ITT population there was a significant decrease in the TSIRHF by 50% within 4 weeks and by 64% within 8 weeks (P<0.0001). The mean total number of hot flushes per day decreased significantly each week from week 1 to 8. The mean number of mild, moderate, severe, and very severe flushes decreased by 46%, 62%, 79%, and 100% over 8 weeks, respectively. The MRS and its somato-vegetative, psychological, and urogenital subscales decreased significantly by 43%, 43%, 47%, and 20% respectively. The treatment was very well tolerated. ***Conclusion:*** A fresh sage preparation demonstrated clinical value in the treatment of hot flushes and associated menopausal symptoms.

Keywords: clinical trial; hot flushes; menopause; sage; *Salvia officinalis*

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BACKGROUND

Menopause is considered a physiological adjustment process to an altered hormonal balance. The "typical" transition to menopause begins with menstrual irregularity at approximately 47 years of age. Intermittent cycling continues for about 4 years, and complete amenorrhea is attained at a median age of 51 years.[1] Worldwide, an estimated 25 million women enter this phase of life every year, with one-third each experiencing no, average, or severe climacteric complaints. Menopausal symptoms can be divided into vasomotor symptoms (sweating, hot flushes, and palpitation), decreased psychic and physical functions (fatigue, depression, fear, forgetfulness, decreased libido, cardiovascular disturbances, and bone and articular alterations), and urogenital symptoms (vaginal dryness, incontinence, and cystitis). The most frequent symptom, hot flushes, is characteristic of up to 88% of women in menopause[2] with an average duration of more than 5 years.[3] Hot flushes have a considerable negative impact on quality of life and may be associated with sleep disorders;[4] one in three women reports sleep problems during menopause. Yet despite the high prevalence of menopausal symptoms in climacteric women in most civilized countries, only half seek medical assistance for it.[2,5] Many are reluctant to rely on hormone replacement therapy (HRT)[6] because of concerns over long-term use,[7] and are inclined to resort to phytotherapeutic treatment options.[8]

The Women's Health Initiative influenced likewise many women to discontinue an already established estrogen therapy,[9] leading many healthcare professionals to consider alternatives to HRT. Despite HRT's effectiveness for symptom reduction and in view of its risks outweighing its benefits, regulatory bodies around the world are now advocating that HRT should only be prescribed at the lowest dose needed and for the shortest possible time.[10-12] As the average duration of menopausal symptoms is 3.5 years[1] with a range from 6 months to 15 years, the continuing need for effective symptom relief has led many women to seek non-medical alternatives.[13]

Sage, a member of the Labiacee family, native to Mediterranean Europe and traditionally used in folk medicine to treat excessive perspiration and sweating in menopause, combines the properties needed to qualify for a promising alternative to treat hot flushes and associated climacteric complaints. However, confirmation via published clinical studies has been lacking, to date. It has been the intent of this study to fill this gap using a thujone-free fresh sage tablet in a once-daily application based on a previous positive response to a fresh plant extract in liquid as well as in a lower-dose tablet form.

Sage has been traditionally applied in cases of excessive sweating[14-16] with fresh extracts regarded as superior with respect to efficacy,[17] and in menopausal complaints, including hot flushes.[18-23] Although sage has been clinically verified to reduce hyperhidrosis up to 52%,[24] there is a lack of published data supporting its use in the treatment of hot flushes and the alleviation of menopause-associated symptoms such as palpitations, insomnia, and mood alterations. In a first clinical study with a sage *(Salvia officinalis)* and alfalfa *(Medicago sativa)* combination product, very good efficacy was demonstrated for two-thirds of the menopausal women examined.[25] An alcoholic tincture of sage also demonstrated considerable efficacy in reducing the frequency of menopausal hot flushes per patient (verum –56.3%, placebo +4.8%) over the treatment period in a randomized, double-blind, placebo-controlled, parallel-group pilot study. The verum medication consisted of 3 × 25 drops of sage tincture daily

for eight consecutive weeks, equaling a dose of 1200 mg fresh sage plant extract daily.[26]

Sage has not only been used traditionally against hyperhidrosis, hot flushes, and night sweats in menopause, but also as a tonic[20] and against mental and physical exhaustion.[27] The elders reflected its manifold benefits in its name "sage" derived from the Latin "salvare," which means to heal or cure. As the perimenopausal period may be associated with a decrease in quality of life caused by a significant decline in perceived physical health and in psychosomatic domains (that is, in nervous and emotional state, self-confidence, work life, and concentration) when compared with premenopausal women,[28] the additional benefit conferred during the transition period by use of a preparation with neuromodulatory efficacy in alleviating depressive moods, nervousness, and irritability has been recognized and was evidenced by a large-scale controlled observational study showing the superiority of a St. John's wort *(Hypericum perforatum)*/black cohosh (BC; *Cimicifuga racemosa*) combination product over BC treatment alone.[29] A significantly modified perception of quality of life remains an important issue in postmenopause.[30,31] Sage as a neuromodulator has a long-standing and clinically substantiated reputation not only for memory enhancement and improvement of cognitive performance,[32] but also as a mood modulator[33] with reported improved self-ratings for alertness, calmness, and contentedness under therapy,[34] and therefore was hypothesized as possibly qualifying for assisting in this essential domain during menopause as well.

Based on these observations, the goal of the present study was to evaluate the safety and efficacy of a once-daily sage preparation complying with the daily dose stipulated by The Complete German Commission E Monographs[35] and European Scientific Cooperative on Phytotherapy[36] in the treatment of menopausal hot flushes and the other climacteric symptoms as embraced by the Menopause Rating Scale (MRS).

MATERIALS AND METHODS

Participants

Patients were recruited from eight general practices in Switzerland from 17 January 2008 to 16 December 2008. The study was approved by the relevant ethical committees and the Swiss health authority, Swissmedic, and was carried out according to the guidelines of Good Clinical Practice and the ethical obligations of the Declaration of Helsinki.

Inclusion criteria were age between 50 and 65 years, at least 12 months since last menstruation, at least five hot flushes daily, and written informed consent. Exclusion criteria included the use of medication with an influence on menopausal symptoms within the last month before the study start, including HRT, plant remedies, and food supplements; allergy to one of the ingredients tested; surgical and medical menopause; serious illnesses, including hyperthyroidism; and participation in another clinical trial in the previous 30 days.

Treatment

Patients received a bottle holding 70 tablets, each containing 280 mg holistic, thujone-free sage spissum extract, extract equivalent 3400 mg tincture of fresh sage leaves, drug extractant ratio 1:17, total (alpha plus beta) thujone <10 p.p.m., sourced from organic cultivations in Switzerland, France, and Germany, verified and manufactured by Bioforce AG (Roggwil, Switzerland; study batch number 01103800). Patients were instructed to

take one tablet daily before strongest flushes for 56 consecutive days. Counting unused tablets at the end of the treatment period checked compliance. In addition, patients documented the application time of the once-daily sage tablet (that is, morning, midday, or evening) in their diaries.

Efficacy Parameters

Patient diary

Efficacy was assessed using the change in intensity and frequency of hot flushes and the change of the total score of the mean number of intensity-rated hot flushes (TSIRHF). The TSIRHF was calculated according to the following formula: TSIRHF=$\sum$(mean number of hot flushes of intensity [i]), with i=1 to 4 (1=mild, 2=moderate, 3=severe, 4=very severe). To this purpose, patients filled out a diary daily during week 0 (baseline) and the following eight treatment weeks, recording the number and intensity of hot flushes over a 24-hour period ranging from 7 a.m. to 7 a.m. or from 12 p.m. to 12 p.m. and allocating each hot flush an intensity using the grading mild, moderate, severe, and very severe according to the intensity classification by Sloan et al.[37]

Menopause Rating Scale: Description of Symptoms

Additionally, the change of the scores of the MRS and related subscales during therapy was evaluated by the treating physician at visit 1 (day –7 before treatment initiation) and visit 3 (day 56). The MRS is a standardized and formally validated scale that has been adopted worldwide to measure the severity of 11 symptoms associated with the climacteric syndrome and to assess the health-related quality of life of menopausal women.

The global MRS score is calculated as the sum of the scores of the following subscales:

- The somato-vegetative subscale, comprising items 1-3 and 11: hot flushes, heart discomfort, sleep problems, and joint and muscular discomfort.
- The psychological subscale, comprising items 4-7: depressive mood, irritability, anxiety, and physical and mental exhaustion.
- The genitourinary subscale, comprising items 8-10: sexual problems, bladder problems, and vaginal dryness.

The intensity of symptoms is rated as follows: 0=no symptom, 1=mild, 2=moderate, 3=severe, 4=very severe.

Safety Parameters

The safety parameters considered were frequency of adverse events, global assessment of tolerability by physician and patient, vital parameters (blood pressure) and laboratory blood values (alanine aminotransferase [glutamic pyruvic transaminase, alanine aminotransferase], aspartate aminotransferase [glutamic oxaloacetic transaminase, alanine aminotransferase], total bilirubin, plasma glucose, serum creatinine, erythrocyte sedimentation rate [1 hour], C-reactive protein, total cholesterol, erythrocytes, mean corpuscular hemoglobin [MCH] concentration, MCH, mean corpuscular volume; hematocrit, hemoglobin, leukocytes, and thrombocytes) determined at visit 2 (day 0, baseline) and visit 3 (day 56).

Statistical Analysis

As this was a safety study, the statistical analysis planned and performed was an intent-to-treat (ITT) analysis of data using descriptive

statistics with a 95% confidence interval and the Wilcoxon signed rank test. The software applied for the analysis was SAS, version 9.2. (SAS Institute Inc., Cary, NC, USA).

RESULTS

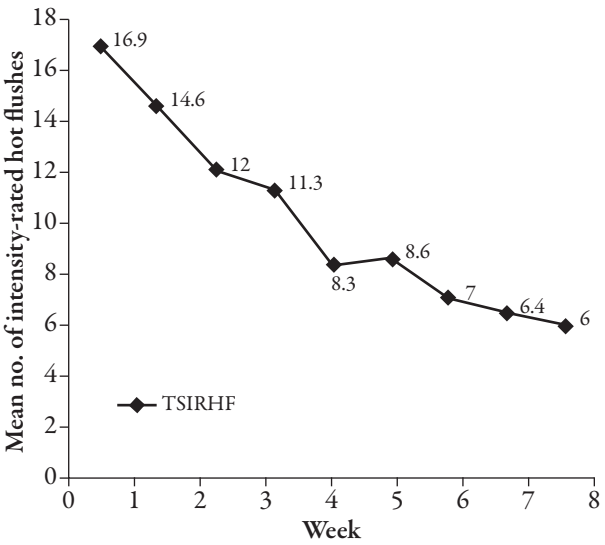
Patient Characteristics

Patients were recruited from eight medical practices in Switzerland. The mean age was 56.4±4.7 years. All treated patients were evaluated according to ITT analysis. A total of 71 patients were included and 69 were analyzed in the ITT population, which comprised all patients for whom intake of the study medication was documented. Two patients were excluded from the ITT population because no intake of tablets had taken place. The change of scores of the MRS and related subscales during therapy was evaluated by the treating physician (Table 1).

Efficacy

Figure 1 summarizes the TSIRHF results, which decreased significantly (by 50% and 64% within 4 and 8 weeks, respectively). The mean total number of hot flushes per day decreased from 9.3±12.2 to 3.8±3.5 after 8 weeks (P=0.0001) and showed a reduction of 29% (to 6.6±6.2) after 2 weeks and 48% (to 4.8±3.6) after 4 weeks of therapy (P=0.0001).

Figure 1. Total score of the mean number of intensity-rated hot flushes (TSIRHF): change from week 0 to week 8 (intent-to-treat population; patient diary).



The reduction from week 0 to week 8 of the mean number of mild flushes was 46%, from 3.7±8.4 to 2.0±2.1 (P>0.05). Moderate flushes were reduced 62%, from 3.9±4.6 to 1.5±2.8

Table 1. Symptoms assessed by the Menopause Rating Scale (MRS; Berlin Center for Epidemiology and Health research).

1. Hot flushes, sweating (episodes of sweating)
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early)
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)
5. Irritability (feeling nervous, inner tension, feeling aggressive)
6. Anxiety (inner restlessness, feeling panicky)
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)
Rating of severity: none=0; mild=1; moderate=2; severe=3; extremely severe=4

(*P*=0.0001); severe flushes were reduced 79%, from 1.4±3.4 to 0.3±0.9 (*P*=0.0001); and very severe flushes were reduced 100%, from 0.3±1.2 to 0.0±0.2 (*P*<0.05) (Figure 2).

In addition, the relative proportion of mild flushes increased from 40% to 53%, while the relative proportions of moderate and severe flushes decreased from 42% to 39% and from 15% to 8%, respectively. The relative proportion of very severe hot flushes was reduced from 3% to 0% (Figure 3).

Figure 2. Mean number of total daily hot flushes per intensity group at week 0 and week 8.

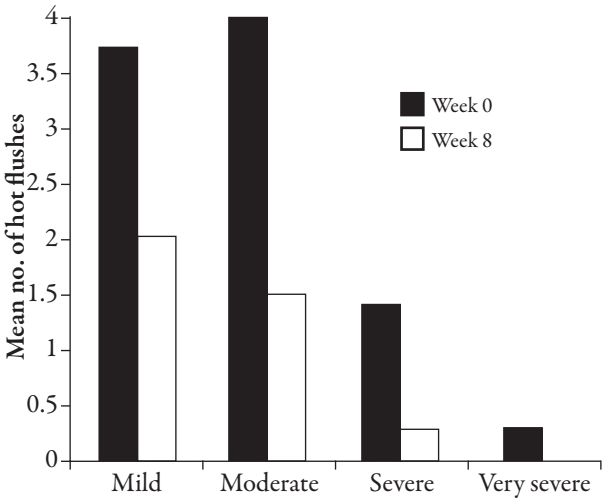
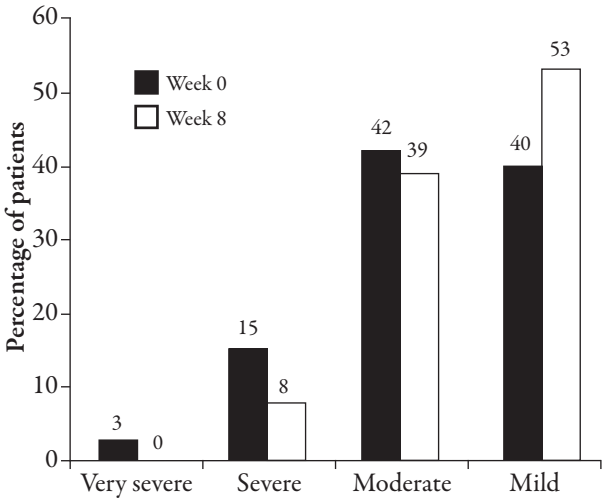


Figure 3. Shift in intensity of hot flushes from week 0 to week 8.

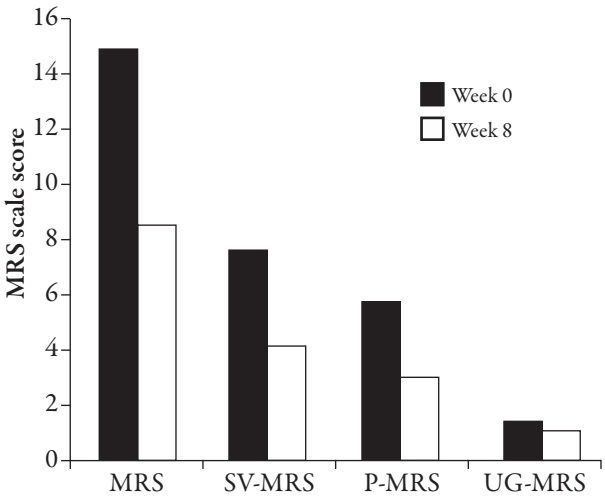


Efficacy was rated as very good or good by 56.3% of physicians and 53.5% of patients (physicians: very good, 36.2% and good, 21.7%; patients: very good, 34.8% and good, 20.3%), as moderate by 17.3% of physicians and 18.8% of patients, and as poor by 24.6% of patients and 23% of physicians.

The results show a statistically significant decrease in the mean global MRS score and all related subscores: the MRS was reduced from 14.9 to 8.6 overall by 6.4±0.9 points (43%) from visit 1 to visit 3 (Wilcoxon signed rank test: *P*<0.0001); the somato-vegetative subscale was reduced by about 3.3±0.4 points (43%) from 7.6 to 4.3 (*P*<0.0001), the psychological subscale was reduced by 2.7±0.5 points (47%) from 5.8 to 3.1 (*P*<0.0001), and the urogenital subscale was reduced by 0.3±0.1 points (20%) from 1.5 to 1.2 (*P*<0.01) (Figure 4).

The results of the Wilcoxon signed rank test are given in Table 2. The mean MRS score was determined for each symptom. With the exception of the symptoms "sexual problems," "bladder problems," and "dryness of vagina,"

Figure 4. Changes in Menopause Rating Scale (MRS) and subscales between week 0 and week 8. P=psychological symptoms; SV=somato-vegetative symptoms; UG=urogenital symptoms.



a significant decrease in mean scores was seen from visit 1 to visit 3 for all MRS symptoms, including heart discomfort, depressive mood, irritability, anxiety, physical and mental exhaustion, and joint and muscular discomfort. The most pronounced decrease (by at least 1 point) was seen for "hot flushes" and "sleep problems" (Table 3).

Safety

A total of 10 adverse events among six patients were observed, of which only two (mild abdominal pain and mild diarrhea in one patient) were related to the study medication. Tolerability was rated as very good or good by 90% of physicians and patients. Evaluation of the laboratory parameters demonstrated a high degree of safety. No significant change was observed in mean leukocyte counts, erythrocyte counts, hemoglobin, hematocrit, mean corpuscular volume, MCH, MCH concentration, erythrocyte sedimentation rate, thrombocyte counts, alanine aminotransferase (glutamic pyruvic transaminase), aspartate aminotransferase (glutamic oxaloacetic transaminase), bilirubin, creatinine, glucose, or cholesterol.

DISCUSSION

As this was an open trial setting over a relatively short period with neither a placebo control nor a natural history arm, hot flush reduction values obtained for placebo arms have been taken into consideration. Screening of placebo-controlled studies revealed that the placebo effect on the reduction in number of hot flushes of a single-blind placebo run-in treatment for 1 month was 17%[38] and ranged from 11% to 40% for double-blind treatment over 3 or 4 months,[39-44] while the placebo effect for depression and overall menopausal symptoms was up to 41%.[44] Compared with these data the observed reduction of the mean total number of hot flushes per day by 30% at week 2, by 50% at week 4, and by 59% at week 8 (P=0.0001) can be considered clinically relevant. Furthermore, this reduction as well as the one of the TSIRHF, which decreased significantly by 50% and 64% within 4 and 8 weeks, respectively, is comparable with the figures obtained for BC *Cimicifuga racemosa* single- or multi-compound preparations, ranging from a 24% reduction at week 6 (BC multicompound preparations, total number of daily vasomotor symptoms[45]) and a 27% reduction at week 8 (BC standard

Table 2. Menopause Rating Scale (global scale, somato-vegetative subscale, psychological subscale, genitourinary subscale), change from visit 1 to visit 3: Wilcoxon signed rank test (intent-to-treat population).

		Actual values			Change		Wilcoxon test
Menopause Rating Scale	Visit	*n*	Mean	Standard deviation	Mean	Standard error	Signed rank *P*
Global scale	Visit 1	69	14.9	6.4			
	Visit 3	66	8.6	6.4	−6.4	0.9	<0.0001
Somato-vegetative subscale	Visit 1	69	7.6	2.4			
	Visit 3	66	4.3	2.7	−3.3	0.4	<0.0001
Psychological subscale	Visit 1	69	5.8	4.7			
	Visit 3	66	3.1	3.8	−2.7	0.5	<0.0001
Genitourinary subscale	Visit 1	69	1.5	1.8			
	Visit 3	66	1.2	1.8	−0.3	0.1	0.0081

Table 3. Menopause Rating Scale (MRS) score for the 11 symptoms of the MRS, change from visit 1 to visit 3: Wilcoxon signed rank test (intent-to-treat population).

	Visit	*n*	Mean	SD	Change		Wilcoxon test *P*
Hot flushes	Visit 1	69	1.8	0.8			
	Visit 3	66	3.1	1.1	−1.2	0.1	<0.0001
Heart discomfort	Visit 1	69	0.9	1.0			
	Visit 3	66	0.7	0.9	−0.3	0.1	0.0022
Sleep problems	Visit 1	69	2.2	1.2			
	Visit 3	65	1.2	1.2	−1.0	0.2	<0.0001
Depressive mood	Visit 1	69	1.3	1.4			
	Visit 3	66	0.7	1.1	−0.6	0.1	<0.0001
Irritability	Visit 1	69	1.6	1.4			
	Visit 3	66	0.9	1.1	−0.6	0.1	<0.0001
Anxiety	Visit 1	69	1.2	1.4			
	Visit 3	66	0.6	1.0	−0.6	0.1	<0.0001
Physical and mental exhaustion	Visit 1	69	1.7	1.2			
	Visit 3	66	0.9	1.1	−0.8	0.1	<0.0001
Sexual problems	Visit 1	69	0.5	0.8			
	Visit 3	66	0.4	0.7	−0.1	0.0	0.0654
Bladder problems	Visit 1	69	0.4	0.8			
	Visit 3	66	0.3	0.8	−0.1	0.1	0.0859
Dryness of vagina	Visit 1	69	0.6	0.9			
	Visit 3	66	0.5	0.8	−0.1	0.1	0.1377
Joint and muscular discomfort	Visit 1	69	1.4	1.2			
	Visit 3	66	0.6	1.0	−0.8	0.1	<0.0001

preparation, average number of hot flushes[46]) to an 81% reduction at week 52 (BC standard preparation, weighted score of hot flushes[47]).

Several studies have shown that sage (*Salvia officinalis* and *S. lavandulaefolia*) possesses neuromodulatory properties.[33] In keeping with these properties is the high response rate found in this study, as measured by the MRS psychological subscale (47%; $P<0.0001$), encompassing depressive mood, irritability, anxiety, and physical and mental exhaustion, which exceeds the already significant decrease in mean global MRS Score and somato-vegetative subscale (43% each; $P<0.0001$), as well as the urogenital subscale (20%; $P<0.01$).

As hot flushes and insomnia are the most prominent menopausal symptoms, it is of particular clinical importance that the most pronounced decrease of all eight significantly reduced menopausal symptoms as assessed via the MRS was seen for "hot flushes" and "sleep problems."

The data support sage's traditionally accredited value in treating not only hot flushes but also climacteric complaints in general. This is the first published clinical study to show efficacy of a sage mono-preparation in relieving both hot flushes and symptoms associated with menopause.

CONCLUSION

Once-daily application of this fresh sage extract demonstrated good clinical value in terms of

safety, efficacy, and tolerability in the treatment of menopausal hot flushes and climacteric symptoms, validated by statistical analyses and the clinically relevant verdict of patients and physicians. The study findings provide a scientific rationale for sage's use in folk medicine, offering a valuable option for patients and healthcare providers seeking alternative approaches to treatment of menopausal hot flushes and climacteric complaints. Further rigorous research to confirm the findings is suggested.

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