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Effect of St John's wort on severity, frequency, and duration of hot flashes in premenopausal, perimenopausal and postmenopausal women: a randomized, double-blind, placebo-controlled study

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Abstract

Objective: Because of a decline in estradiol levels, premenopausal, perimenopausal, and postmenopausal women experience symptoms related to vasomotor instability. Certain plants have been found to have molecular components that are identical in structure and function to human hormones. We conducted this study to compare the efficacy of St John's wort with that of placebo in women with hot flashes.

Methods: A total of 100 women participated in a clinical trial conducted in an academic medical center in Shiraz-Iran. Women were treated with St John's wort extract or placebo for 8 weeks. Climacteric complaints were evaluated by using the Blatt-Kupperman Index at two follow-up visits. Statistical analysis was carried out by using descriptive statistics and multivariate analysis.

Results: The mean age of the participants was 50.4 years. Both groups responded to the interventions, and the within-group differences in frequency, duration, and severity of hot flashes were statistically significant ($P < 0.05$). The difference in duration of hot flashes between groups was not significant on the 4th week of intervention ($P = 0.27$); however, it was statistically significant between the two groups on the 8th week of treatment ($P < 0.001$). The fall-off in frequency of hot flashes on the 4th and 8th weeks of intervention was more evident in women receiving St John's wort, and the differences between groups were statistically significant ($P = 0.005$ and $P < 0.001$, respectively). Furthermore, comparing both study groups, we showed that the decrease in the severity of flashes in women who received St John's wort was more evident on the 4th and 8th weeks ($P = 0.004$ and $P < 0.001$, respectively).

Conclusions: St John's wort can be used as an effective treatment for the vasomotor symptoms of perimenopausal or postmenopausal women.

Key Words: St John's wort – Severity – Frequency – Duration – Hot flashes – Menopause.

Estradiol levels decline intermittently during the premenopausal transition and permanently after menopause. As a consequence, women experience symptoms related to vasomotor instability, neurocognitive dysfunction, accelerated bone loss, urogenital atrophy, and cardiovascular disease. Most women at the climacteric age of 45 to 60 years experience climacteric complaints.[1] Hot flashes are the most common symptom of menopause, due to vasomotor instability, and occur in most postmenopausal women, with a prevalence of 67% to 80%.[2]

Until recently, the standard treatment for menopausal symptoms was estrogen + progesterone therapy.[3] Despite the well-known benefits of hormone therapy (HT), it can be complicated by potential serious adverse effects such as irregular uterine bleeding, mastalgia, nausea, migraine, weight gain, hydric retention, and fear of breast cancer.[4,5] Thereby, most premenopausal, perimenopausal, and postmenopausal women look for nonhormonal therapies, such as herbal therapy, to manage their hot flash symptoms. Certain plants (soy, black cohosh, and St John's wort, for instance) have been found to have molecular components that are identical in structure and function to human hormones and can be used in these preparations. These herbs can provide symptomatic relief of hot flashes, night sweats, irritability, and depression.[6]

St John's wort (*Hypericum perforatum*) is a well-known herb, which has been used for more than 2,000 years for a variety of "nervous disorders." The efficacy and safety of St John's wort for the treatment of mild to moderate

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depressed mood disorders have been demonstrated by numerous clinical studies.[7-9] Its preparations include hypericin along with flavonoids, xanthone derivates, plant acids (chlorogenic acid and caffeic acid), tannins (catechin), and the phloroglucin hyperforin.[10] Many women have adopted St John's wort as a natural alternative to hormone therapies for their psychological complaints.[11] In addition, this herb contains compounds called phytoestrogens, which can be used as an alternative to estrogen in women having a contraindication to use of female sex hormones.[12]

The aim of this trial was to determine the actual efficacy of a standardized extract of St John's wort for the treatment of vasomotor symptoms (VMS). We hypothesized that St John's wort extract will produce a superior effect in contrast to placebo in the treatment of hot flashes.

METHODS

This was a randomized, double-blind, placebo-controlled clinical trial comparing the efficacy of St John's wort with that of placebo in women experiencing hot flashes. Women for this study were recruited at the outpatient academic medical center in Zeinabieh Hospital in Shiraz, Iran, in 2008. The Medical Research Ethics Committee of Shiraz University of Medical Sciences approved the trial protocol before study initiation. Informed consent was obtained through the provision of an information leaflet coupled with verbal reassurance that participation was voluntary and that the participant could withdraw at any time. In addition, all participants were guaranteed confidentiality of information during and after the study.

Women between 45 and 55 years of age experiencing hot flashes volunteered to take part in this study. Inclusion criteria were (1) being naturally premenopausal (regular menstrual cycles during the last 3 mo), perimenopausal (3-11 mo of amenorrhea or increased menstrual irregularity if still cycling), or postmenopausal (≥12 mo of amenorrhea); (2) having untreated complaints for at least 2 months; (3) having no cancer or a history of breast cancer; (4) experiencing moderate to severe hot flashes at least once a day; (5) having no illnesses creating hot flash–like symptoms; (6) presenting with a serum follicle-stimulating hormone level of more than 40 mIU/mL by means of routine hormonal assessment; (7) experiencing hot flashes for at least 12 weeks; and (8) having three or more hot flashes per day.

Main exclusion criteria were (1) having undergone treatment with sexual hormones, nonhormonal climacteric drugs, or any treatment to alleviate climacteric symptoms in the last 12 weeks before study entry, (2) having undergone treatment with chemical or plant-derived medicines in the last 12 weeks before study entry, (3) having undergone bilateral oophorectomy, (4) having severe diseases (eg, of the heart, liver, kidney, or alimentary system or metabolic diseases) or an abnormal thyroid-stimulating hormone value that could mimic climacteric complaints or the actual or expected treatment or that could interfere with the study objectives, and (5) smoking or drinking alcohol or substances containing caffeine.

Fifty women were required in each treatment group for 80% power at the 95% confidence level to find a difference of 31% in the severity, duration, and frequency of hot flashes.

The trial substances, St John's wort extract (Hypiran, Poursina Pharmaceutical Mfg Co, Tehran, Iran) and placebo drops, had identical external properties. There was no difference in color, taste, or smell between treatment and placebo drops. The St John's wort drops contained hypericin 0.2 mg/mL. The placebo consisted of distilled water.

A total of 236 women were screened, 136 of whom did not receive the study medication because of exclusion criteria or noncompliance with the inclusion criteria. Therefore, 100 women were included. Using a random table, participants were randomly allocated to either the St John's wort therapy or placebo at the first visit (baseline) in the following way: we listed all of the eligible people and assigned each member of the population a numerical label. Then, using a random table, we pointed a finger on the table to choose an arbitrary and random starting point. The woman who possessed that number was the first participant in the treatment group. Next, we moved across the row of numbers to the very next number to select the first participant in the control group. If the next number was less than 100, it was taken as a sample. We continued and assigned every other number to each of the groups until the two groups had 50 participants each.

Fifty women received St John's wort, and the remaining 50 individuals received placebo. All participants were supposed to take the drops three times per day, in the morning, in the midday, and at night, each time taking 20 drops, for two consecutive months. The dose corresponded to the dose recommended in the Summary of Product Characteristics of the tested product. The amount of treatment/placebo used by each woman was checked at each follow-up visit.

Clinical examinations and interviews were performed before commencement of treatment and on the 4th and 8th weeks of treatment. Treatment effectiveness was assessed at the 4th and 8th weeks using the Blatt-Kupperman Index.[14]

This assessment tool of climacteric symptoms is based on the most common complaints, which include hot flashes, sweating, sleep disturbances, nervousness, depression, fatigue, vertigo, arthralgia, headache, tachycardia, and vaginal dryness. The symptom findings are converted into a summary numerical figure based on severity, graded as 0, do not exist; 1, mild; 2, moderate; and 3, severe. This index is often modified, depending on the outcomes being measured in the study, and is widely used in clinical studies measuring menopausal changes.[15]

Among the various symptoms that could have been evaluated by this tool, we measured the severity of hot flashes. We also asked women to report the frequency and duration of their hot flashes during 24 hours at baseline and 4 and 8 weeks after treatment. Women were expected to report adverse events, if any, at the two follow-up visits.

Data analysis was carried out using SPSS, version 10 for Windows. We used descriptive statistics and multivariate

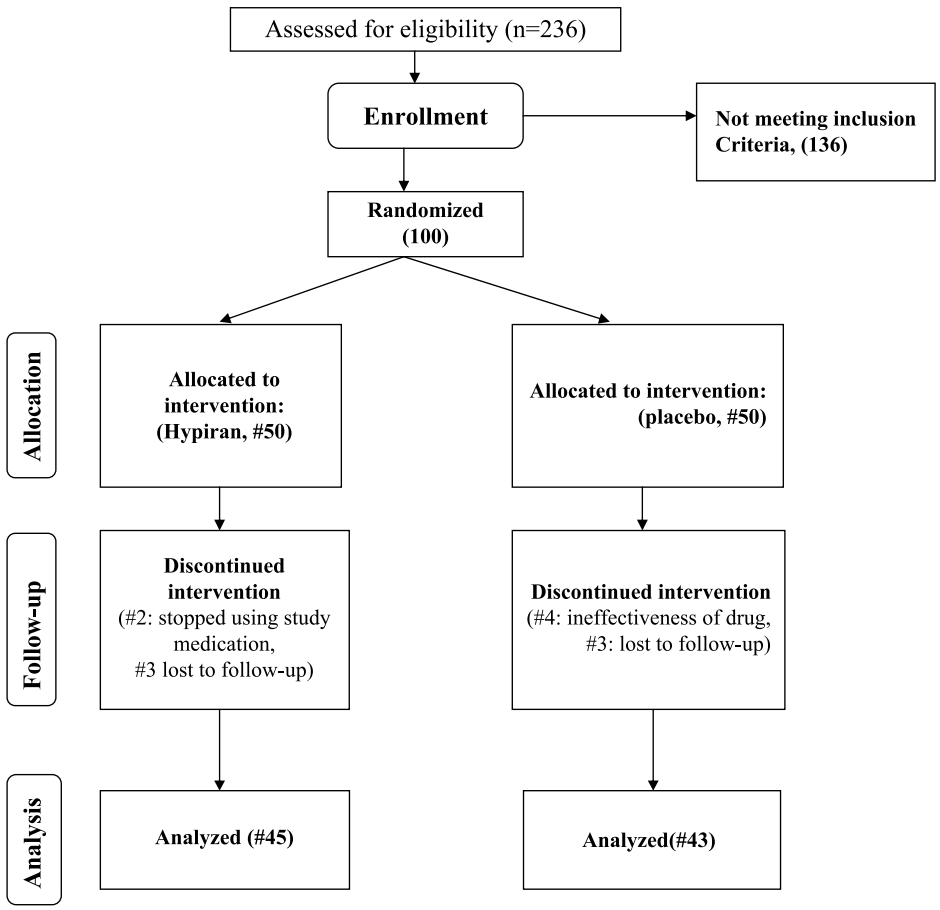

FIG. 1. The flow of participants through each stage of the randomized trial.

analysis to compare the frequency, duration, and severity of hot flashes within and between groups. Furthermore, we used a χ^2 test to determine the relationship between demographic status and the severity of hot flashes. A *P* value was regarded as statistically significant if it was lower than 0.05.

RESULTS

Of the initial 100 women (50 in the treatment group and 50 in the control group), 88 completed the trial (45 in the treatment group and 43 in the control group). Five women in the treatment group did not finish treatment (two stopped using study medication and three were lost to follow-up) and seven women in the placebo group discontinued medication (four of them because of ineffectiveness of the drug and three were lost to follow-up; Fig. 1). However, data from 100 women were available for the primary intention-to-treat analysis.

Sociodemographic status was not statistically different between those who finished the study and those who did not. The demographic status (age, weight, severity, and frequency and duration of hot flashes per 24 h) of both study groups was evaluated at baseline, and there were no statistically

TABLE 1. *Demographics of the treatment and placebo groups*[a]

Group characteristic	St John's wort (n = 50)	Placebo (n = 50)	*P*
Age, y	50.52 ± 3.72	50.29 ± 3.52	0.411
Weight, kg	70.3 ± 5.48	68.98 ± 4.66	0.231
Parity (no. children)	3.6 ± 4.67	2.67 ± 6.01	0.086
Blood pressure, mm Hg	13.45 ± 3.7	13.98 ± 1.3	0.634
Severity of hot flashes per 24 h	2.31 ± 0.66	2.3 ± 0.7	0.407
Duration of hot flashes (min per 24 h)	21.68 ± 4.67	20.46 ± 4.67	0.396
Frequency of hot flashes (per 24/h)	3.88 ± 0.85	3.88 ± 0.76	0.099
Follicle-stimulating hormone, mIU/mL (at baseline)	63.4 ± 12.76	65.1 ± 10.67	0.101

[a]Values are given as mean ± SD.

TABLE 2. *Mean changes in the number of hot flashes during 24 hours in both groups*

	Baseline		4th week of intervention		8th week of intervention	
Frequency	Mean	SD	Mean	SD	Mean	SD
St John's wort	3.88	0.85	2.84	0.99	1.8	1.03
Placebo	3.88	0.76	3.37	0.69	2.65	0.81
Significance[a]	$P = 0.526$		$P = 0.005$		$P < 0.001$	

[a]Tukey post hoc comparison showed that the differences between the St John's wort and placebo groups were statistically significant in frequency on the 4th and 8th weeks of intervention.

TABLE 3. *Mean changes in the duration of hot flashes during 24 hours in both groups*

	Baseline		4th week of intervention		8th week of intervention	
Duration, min	Mean	SD	Mean	SD	Mean	SD
St John's wort	21.68	4.67	16.15	5.01	10.71	5.8
Placebo	20.46	4.67	18.02	4.38	15.69	4.56
Significance[a]	$P = 0.27$		$P = 0.085$		$P < 0.001$	

[a]Tukey post hoc comparison showed that the differences between the St John's wort and placebo groups were statistically significant in duration on the 4th and 8th weeks of intervention.

TABLE 5. *Adverse events recorded in the two groups during the intervention*[a]

	St John's wort (n = 42)		Placebo (n = 39)		
	4th week	8th week	4th week	8th week	*P*
Headache	2 (18.18)	1 (25)	5 (41.67)	2 (50)	0.485
Abdominal pain	2 (18.18)	0	4 (33.33)	1 (25)	0.133
Lethargy	7 (63.64)	3 (75)	3 (25)	1 (25)	0.151
Total	11 (100)	4 (100)	12 (100)	4 (100)	—

[a]Values are given as no. (%).

significant differences in all baseline parameters between groups (Table 1) There was no statistically significant relation between demographic status and the severity, frequency, and duration of hot flashes.

The mean frequency of hot flashes at the baseline visit was somehow similar in both study groups, and there were no significant differences between groups (ranging from two to five onsets per 24 h). The fall-off in the frequency of hot flashes per day in women receiving St John's wort was evident during the 1st and 2nd months of intervention. Nevertheless, women showed more improvement in their frequency of flashes during the 2nd month ($P < 0.05$). In the placebo group, there was no statistically significant change in the frequency of hot flashes during the 1st month of intervention. However, frequency of flashes was improved the most during the 2nd month of intervention ($P < 0.05$). During both months of intervention, women who had used St John's wort showed more improvement in their frequency of flashes than the placebo-receiving group did ($P < 0.05$; Table 2).

Both study groups were similar in terms of duration of hot flashes before intervention (ranging from 10 to 32 min per 24 h). Both groups responded to interventions, their duration of flashes decreased during the 1st month, and both of them were similar in terms of the response to treatment. On the other hand, the difference between groups was statistically significant on the 8th week of treatment, and the decline in the duration of hot flashes was much more remarkable in the corresponding St John's wort arm ($P < 0.05$; Table 3).

As shown in Table 4, both study groups were similar in the severity of hot flashes before the intervention (ranging from one to three per 24 h). The severity of flashes in women who received St John's wort was abated during the 2 months of intervention. This reduction was much more noteworthy in the 2nd month, and there were statistically significant differences from the 1st month to the 2nd month ($P < 0.05$). Women who received placebo did not show significant alteration in the severity of hot flashes during the 1st month of intervention. However, during the 2nd month, they showed more notable improvement than they did in the 1st month ($P < 0.05$). Furthermore, there was a significant difference between the two study groups during intervention, and women who received St John's wort felt more comfortable than did those who were on placebo.

In the treatment groups, 23 and 8 participants reported adverse events in the 4th and 8th weeks of treatment, respectively. Lethargy was the most prevalent reported adverse event. No significant differences were found in the adverse events caused by the two preparations (Table 5).

TABLE 4. *Mean changes in the hot flash severity score during 24 hours in both groups*

	Baseline		4th week of intervention		8th week of intervention	
Severity	Mean	SD	Mean	SD	Mean	SD
St John's wort	2.31	0.66	1.7	0.57	0.93	0.44
Placebo	2.3	0.7	2.1	0.62	1.7	0.62
Significance[a]	$P = 0.729$		$P = 0.004$		$P < 0.001$	

[a]Tukey post hoc comparison showed that the differences between the St John's wort and placebo groups were statistically significant in severity on the 4th and 8th weeks of intervention.

DISCUSSION

VMS, such as hot flashes and night sweats, are the most bothersome symptoms of menopause and affect an estimated 75% of women older than 50 years. Although estrogen therapy and estrogen + progestin therapy remain the treatments of choice for women with VMS, recent HT trials have changed our understanding of the risks and benefits of these therapies.[16] The availability and use of alternatives to HT, including over-the-counter supplements, phytoestrogens, and homeopathic medicines, have grown dramatically during the past decade. Furthermore, it is believed that dietary changes that include a higher consumption of phytoestrogens may relieve hot flashes.[17,18]

The purpose of this study was to evaluate the effect of St John's wort extract on menopausal VMS.

There were some limitations while conducting this study. The regular and complete use of drugs was out of our control. In addition, this was a self-report study, and we had to rely on the participants' claims. Because the standard of care for menopausal symptoms is HT, it would have been helpful to include an arm assigned to HT so that the effect of St John's wort versus that of standard of care could have been evaluated.

Despite these shortcomings, we found it fair to conclude that our study was a powerful one because of the recruitment method and randomization. In addition, a minimal number of participants were lost to follow-up.

Various previous clinical trials used St John's wort along with other herbs to relieve miscellaneous menopausal symptoms and psychological problems. Briese et al[19] evaluated the usage pattern, effectiveness, and safety of black cohosh (*Cimicifuga racemosa*) alone or in a fixed combination with St John's wort on menopausal symptoms in general clinical practice. They pointed out that a fixed combination of black cohosh and St John's wort was superior to black cohosh alone in alleviating climacteric mood symptoms. Uebelhack et al[20] investigated the efficacy of the fixed combination of black cohosh and St John's wort extracts in women with climacteric complaints with a pronounced psychological component. They demonstrated that this fixed combination was superior to placebo in alleviating climacteric complaints, including the related psychological component.

Most of the former studies used this herb along with other phytoestrogens, and these studies attributed the improvement of mood disorder to St John's wort. They claimed that a fixed combination of black cohosh and St John's wort would be more effective in alleviating climacteric mood symptoms. As a matter of fact, the efficacy of this herb in relieving menopausal symptoms is probably due to separate actions: first, because of its phytoestrogenic properties, the herb helps improve the mood changes that are often associated with the hormonal changes that come with menopause. Second, the herb increases the levels of serotonin in the brain. Gynecologists have long used medications that increase serotonin as an "off-label" treatment to relieve hot flashes.[21,22] It has been taken for granted that the improvement in the psychological status of women might have been due to the positive effect of St John's wort on hot flashes. Actually, women felt more comfortable and relaxed when they did not experience severe hot flashes, and, on the other hand, they became more anxious and nervous when hot flashes commenced.

In a recent study, Al-Akoum et al[23] evaluated the effect of *H perforatum* extract (St John's wort extract) compared with that of placebo on symptoms and quality of life of symptomatic perimenopausal women. They declared that *H perforatum* might be an efficient treatment to improve quality of life and hot flashes in symptomatic perimenopausal women. The results of our study were similar to theirs, and we showed that after 4 weeks, the St John's wort therapy caused a drop of 26.8% in the frequency of hot flashes, 25.6% in duration of hot flashes, and 26.5% in severity of hot flashes, whereas the placebo caused a reduction of only 13.2% in the frequency of hot flashes, 11.9% in the duration of hot flashes, and 8.7% in the severity of hot flashes. On the 8th week of treatment, the frequency of hot flashes in the St John's wort arm dropped by 53.7%. The duration and severity of hot flashes fell by 50.6% and 59.8%, respectively, whereas in the placebo group, the frequency, duration, and severity of hot flashes dropped by 31.8%, 23.4%, and 26.1%, respectively. As can be seen, the most important changes were perceived in the frequency and duration of hot flashes. Nevertheless, Krebs et al[24] stated that phytoestrogens did not improve hot flashes or other menopausal symptoms. In addition, Lethaby et al[25] claimed that the effectiveness of phytoestrogens in the alleviation of menopausal symptoms was not evidenced and there was no significant benefit for phytoestrogens.

In our study, the influence of both preparations on VMS was more significant in the 2nd month than that in the 1st month of intervention. Therefore, we assumed that if the duration of treatment with St John's wort had lasted for more than 2 months, wider changes would have been observed in the frequency, duration, and severity of hot flashes. However, long-term safety and side effects ought to be regarded.[26]

Whereas we found out that good tolerability was reflected in the high rates of satisfaction and compliance among women in both the St John's wort and placebo groups (84% and 57%, respectively), Tempfer et al[27] claimed that the use of phytoestrogens in menopausal women should be restricted only to those presenting with mild to moderate VMS in early natural postmenopause. On the other hand, it has been reported that interactions between St John's wort and certain prescribed medicines (including warfarin, cyclosporin, theophylline, digoxin, HIV protease inhibitors, anticonvulsants, selective serotonin reuptake inhibitors, triptans, and oral contraceptives) should be regarded.[28]

We suggest that more biochemical studies be performed to realize the exact mechanism of action of this medicinal herb. Furthermore, future trials in different study populations and with different daily doses of St John's wort extract are needed to make definite decisions on the use of St John's wort for improving VMS of menopause.

CONCLUSIONS

We performed this study to evaluate the effect of St John's wort extract on menopausal hot flashes. The positive influence of St John's wort on hot flashes offers an effective treatment for VMS associated with the hormonal fluctuation of perimenopause or menopause.

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