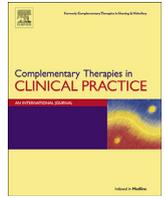




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The effect of Hop (*Humulus lupulus L.*) on early menopausal symptoms and hot flashes: A randomized placebo-controlled trial

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ABSTRACT

Objective: This study aimed to evaluate the efficacy of Hop on early menopausal symptoms and hot flashes.

Methods: In this randomized controlled trial, 120 women were randomly allocated into two groups, receiving the Hop or placebo tablets for 12 weeks. Early menopausal symptoms were assessed using Greene scale and hot flashes were recorded in a diary before, and 4, 8 and 12 weeks after intervention. **Results:** The mean Greene score was significantly lower in the Hop group than the placebo group at the end of weeks 4 (adjusted difference: -10.0, 95% confidence interval: -11.1–-8.9), 8 (-18.6, -20.1–-17.1) and 12 (-23.4, -25.1–-21.6). The number of hot flashes was significantly lower in the Hop group than the control group during the weeks 4 (-8.4, -9.8–-7.1), 8 (-17.1, -14.9–-19.3) and 12 (-23.8, -21.1–-26.4).

Conclusions: Hop effectively reduced the early menopausal symptoms.

Clinical trial registration: This study was approved (code 91209) by the Ethic Committee of Tabriz university of Medical Sciences and registered at the Iranian registry of clinical trials, with IRCT 2013010110324N7 on April 2013.

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1. Background

Menopause refers to permanent cessation of menstruation that occurs averagely at age 51; this period is characterized by amenorrhea [1]. The most common and specific symptom of menopause is hot flashes. The symptoms occur periodically as flushing, sudden sweating and chills, palpitation, anxiety, feeling pressure in head and chest, feeling flushed and intense heat, nausea, choking, and failure to focus [2]; these can disturb social activities, leisure, sleep, mood, focus, communication, sexual activity, and quality of life [3].

According to a large cross-sectional study in America, 57% of postmenopausal women and 49% of women in the premenopausal period showed significant symptoms of hot flashes [4]. In a study in Iran, 80% of women experienced moderate to severe and 10% mild flushing [5]. Hot flashes occur in approximately 75% of women during perimenopause and in most women last for 1–2 years after

menopause, however it can continue up to 10 years or more [6].

The average life expectancy of women in Iran is estimated as 74.6 years [7] and according to the World Health Organization-2011, life expectancy of women at birth in 46 countries is more than 80 years [8], therefore, by increasing life expectancy, probably more women will encounter with menopausal complications such as increased blood cholesterol, cardiovascular diseases, osteoporosis, bone fractures, and even Alzheimer [9]. Therefore, study and treatment of menopausal problems has gained more importance.

Hormone therapy is a method of relieving early symptoms of menopause, but it may be associated with side effects and risks such as stroke, thromboembolic events, breast cancer, and vascular diseases, thus hormone-taking women need to be followed continuously [10]. According to a very large study performed for 5.6 years in 40 centers in the United States and comprised more than 27 thousand 50–79 years old postmenopausal women, combined hormone therapy is not recommended to treat symptoms of menopause [11]. Therefore, the use of alternative and complementary therapies is somewhat expanded [12]. Among alternative

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and hormonal treatments, herbal medicine including phytoestrogens (estrogen-like compounds) has gained a special place in treatment of menopausal symptoms [2]. According to a research carried out in Iran, only 9% of menopausal women used hormone therapy [13].

Phytoestrogens with three main categories of flavonoid, coumestran, and lignan are herbal compounds with estrogenic activity. Their chemical structure consists of two phenolphthaleins which can bind to estrogen receptor [14]. Phytoestrogens reduce the risk of cardiovascular diseases, breast and endometrial cancer, and osteoporosis, relief menopausal symptoms, especially hot flashes, and improve memory performance and sleep patterns. Low incidence of cardiovascular diseases in part of Asian population who consume phytoestrogens-containing diet demonstrates their protective effects [2,15].

Hop is a plant that contains phytoestrogens including prenylnaringenin as the most powerful phytoestrogen known to date [16]. Hop is 8 times stronger than other herbal estrogens. These phytoestrogens can bind to both estrogen receptors in the body and exert anticancer and antioxidant activities [17]. Hop is a dioecious, perennial, herbaceous climbing plant in the Cannabaceae family with thick fleshy roots, underground stems, and opposite, serrated leaves consisting of 3–5 unequal lobes. Its organs are covered with coarse fibers (containing lupulin) and it contains linalool, tannin, and resin [3,18]. When taken orally, the herb has hormonal activity [19].

The impact of hop on symptoms of menopause has been studied in a placebo-controlled double-blind study in Belgium (2006) which reported its effect on reducing vasomotor and other menopausal symptoms after 6 and 12 weeks. However, the drug was prescribed in this study as 100 µg extract in capsule. It was also stated that no specific dosage is identified currently to reduce symptoms and further research seems necessary in this regard [20]. Thus, we decided to investigate the impact of hop on early symptoms of menopause (primary outcomes) and hot flashes number (secondary outcome).

2. Methods

2.1. Study design and participants

This study was a double-blind controlled randomized clinical trial. It was performed in 2013 in health centers of Tabriz-Iran, on 40–60 years postmenopausal women (minimum 12 months and maximum 5 years after the last menstrual bleeding) and premenopausal women (with less than 12 periods during the last 12 months) who complained of hot flashes and had Greene scale scores of 15 and 42.

Exclusion criteria were illiteracy and inability to answer questions, not having cell phone for follow-up, consumption of sulfonamides, methotrexate, triamterene, sulfasalazine, estrogen, phenytoin, anxiolytics, anti-depressants, daily medicines and multivitamin, hormone therapy, use of OCP during the last 3 months, complementary alternative herbs to relieve vasomotor symptoms during the last month, hormone therapy contraindications including suspected or diagnosed breast or endometrial cancer, abnormal and undiagnosed genital tract bleeding, thromboembolic active disorders, liver or gallbladder active disease, lactose intolerance, and use of anti-thyroid drugs and other traditional medicines such as flushing-causing drugs (such as breast cancer medicines such as Letrozole, Raloxifene, Amlodipine, Bethanecol, Desmopressin and Calcitonin).

According to the study of Yasui et al. [21], and considering $m_1 = 18.3$ (mean of total score of menopause early symptoms before intervention), $m_2 = 15.5$ (assuming a 15% reduction in total

score of menopause early symptoms), and $SD_1 = SD_2 = 4.9$, the sample size was calculated as 54 people for each group and considering the possibility of 10% loss, 60 subjects were estimated finally for each group.

2.2. Data collection tools

Data collection tools included a demographic questionnaire, the Greene Scale, and the recording checklist of hot flashes number.

The Greene Scale was devised by Professor Greene in Scotland and its reliability and validity has been proved [22]. The scale independently measures menopause-related mental, physical, and vasomotor symptoms. It includes 21 questions related to symptoms of menopause and each symptom is scored by the answerer as follows; no symptom as zero, little symptom as 1, moderate symptom as 2, and severe symptom as 3. Items 1–11 include psychiatric symptoms and are divided into two parts of anxiety (items 1–6) and depression (items 7–11), items 12–18 measure menopause physical symptoms, items 19 and 20 measure vasomotor symptoms, and item 21 measures sexual dysfunction [23,24].

2.3. Sampling

For sampling, at first 20, out of 90, health centers and bases were selected in Tabriz city-Iran with the highest number of patients, however, it was tried to select centers with different socio-cultural conditions. Then all premenopausal women were selected through their file (women up to menopausal age have a record in health centers and bases) and postmenopausal women were presented to the researcher by health liaisons; the researcher called and invited these subjects if they were qualified. In addition, health care employees were asked to inform the researcher in case of refers of eligible women. At the first visit, a written informed consent was obtained from participants after explaining the objectives and methodology of the study. The pretest questionnaires (demographic questionnaire and the Greene Scale) were completed by the participants; they were enrolled in the study if the score of the Greene Scale was more than 15 and less than 42.

2.4. Intervention

The participants were divided into two groups of intervention and control through randomized blocking with block sizes of four and six and allocation ratio of 1:1. To conceal the allocation of drug and placebo, they were put in closed opaque envelopes which were numbered serially. Each participant received three small envelopes each containing a month's supply of medication; these small envelopes were put in large opaque pockets numbered consecutively. Blocking and preparation of the pockets were performed by a person uninvolved in sampling and data analysis.

Each hop tablet is about 650 mg that contains 500 mg of Hop plant (the powdered flowering part of the plant, corymb), in which, it's contains 100 µg of the active ingredient. The main ingredient of the tablet is powdered hop plant's corymb that contains phytoestrogen. Hop tablets (powdered inflorescence of Hop, 5% gelatin solution, and avicel) and placebo (powdered lactose, 5% gelatin solution, and avicel) were similar in terms of shape, size, color, and odor. In order to achieve these similarities, red and blue permitted food additives were used, which led to consistent flavor and aroma.

Thus the data collectors, the participants, and the data analyzers were unaware of the type of intervention and the allocation of the individuals in the groups.

All participants in the intervention group received a Hop tablet daily for 90 days. Prior to intervention, a small pocket containing Hop or placebo and the checklist of hot flashes number during the

fourth week were provided to the participants. They were reminded to bring the drug pocket and the checklist of hot flashes number of the fourth week in the next visit, 4 weeks after the intervention. The Greene Scale was completed again and a second pocket containing placebo or Hop and the checklist of hot flashes number during the eighth week were provided to the participants. The next follow-up was at the end of the eighth week; the second pocket and the checklist of hot flashes number of the eighth week were taken and the Greene Scale was completed; a third pocket and the checklist of hot flashes number during the twelfth week were provided. The last follow-up was at the end of the twelfth week and the checklist of hot flashes number during the twelfth week and the pockets of consumed tablets were taken and the Greene Scale was completed. At the 2nd, 6th, and 10th weeks, the participants were called to emphasize taking medication regularly and completing the checklist of hot flashes number.

2.5. Statistical analyses

The data were analyzed using SPSS. The normality of the quantitative data was reviewed through Skewness and Kurtosis test; the variables were normal for Greene total score at pre-intervention and the weeks 4 and 12 post-intervention, for the anxiety score at pre-intervention and the weeks 4 and 8 post-intervention, for the depression score at pre-intervention and the weeks 8 and 12 post-intervention, and for the physical score at pre-intervention and the week 4 post-intervention. However, the vasomotor and sexual scores at pre-intervention and three times of post-intervention evaluations, the anxiety score at the week 12, the depression score at the week 4 post-intervention, and the physical score at the weeks 8 and 12 post-intervention had not a normal distribution.

In case of normal variables, independent t-test was used to compare the mean scores of the two groups at pre-intervention,

and ANCOVA test with adjusting for baseline score was used to compare the mean scores at the weeks 4, 8 and 12 post-intervention. In case of abnormal variables, mean scores between the two groups was compared at pre-intervention using Mann–Whitney test, while at post-intervention, the difference between the mean scores at the weeks 4, 8 and 12 was calculated with the pre-intervention score and then the difference of means was evaluated by Mann–Whitney test, which results was identical to ANCOVA test. In addition to the mean, median (25th percentile–75th percentile) was also calculated.

3. Results

All 120 participants were cooperated until the end of study and fully completed the questionnaires, thus 120 patients were analyzed (Fig. 1). No one consumed another drug to control menopausal symptoms. There was no statistically significant difference ($p > 0.05$) between the groups in terms of demographic characteristics (Table 1), total score of the Greene Scale and its components, as well as the number of hot flashes before the intervention (Table 2).

About two-thirds (66%) of the subjects in each group had an age range of 40–50 years and about half of the participants (47%) had a BMI of 25–29.9. About half of them (44%) had an elementary level education and about a quarter of their spouses had a secondary and high school level education (24.0% each). Slightly more than three-quarters of the participants (87%) in both groups were married, a case in the intervention group was single, and the rest were widowed. The majority of women (85%) were housewives. About half of the women (49%) had an exercise activity, mostly daily walking. Over 90% of them did not drink colas. Any participant was smoker. Only 6 cases were taking calcium and vitamin D. More than half of the women (57%) gave birth 3–5 times. The mean (SD) duration of menopause was 37.9 months in the postmenopausal women in the

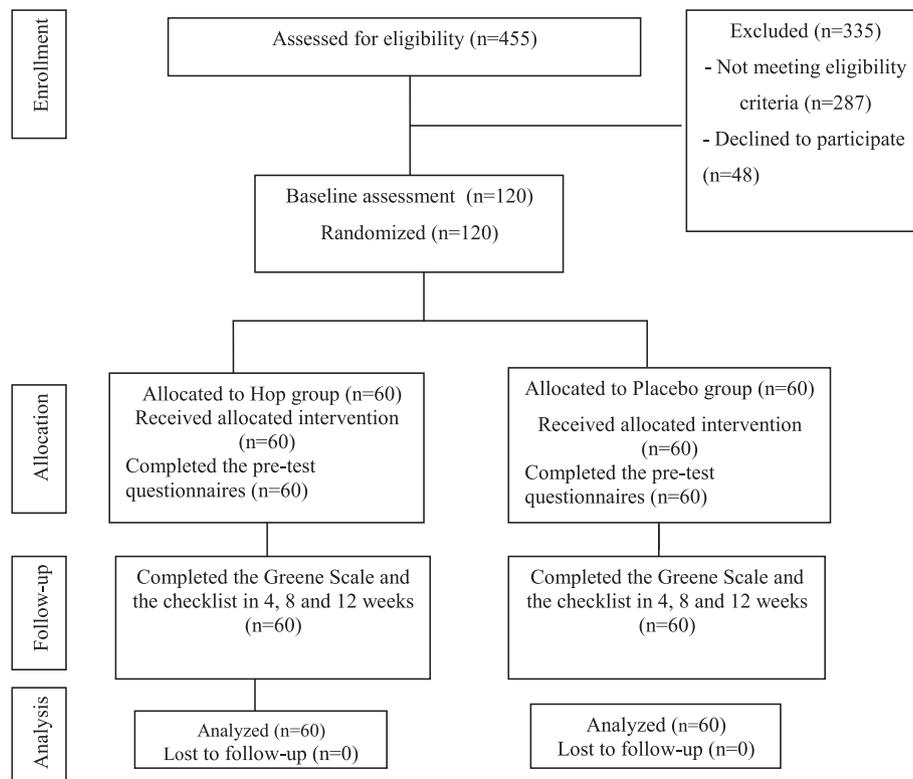


Fig. 1. Flowchart of the study.

Table 1
Demographic characteristic of the participants in the treatment (Hop) and control (placebo) groups.

Variables	Hop (n = 60) number (percent)	Control (n = 60) number (percent)	p
Age (year)			
40–50	42 (70.0)	37 (61.7)	0.336 ^b
More than 50	18 (30.0)	23 (38.3)	
Mean(SD) ^a	49.8 (4.17)	50.5 (5.0)	0.064 ^c
Postmenopause	30 (50.0)	30 (50.0)	1.000 ^b
Premenopause	30 (50.0)	30 (50.0)	
Education			
Elementary	26 (43.3)	27 (45.0)	0.977 ^d
Secondary	11 (18.3)	19 (31.7)	
High school	17 (28.3)	9 (15.0)	
University	6 (10.0)	5 (8.3)	
Duration of menopause (month)			
Less than 24	9 (30.0)	14 (46.7)	0.414 ^b
More than 24	21 (70.0)	16 (53.3)	
Mean(SD) ^a	37.9 (19.7)	36.5 (29.0)	0.566 ^c
Parity			
≤3	19 (31.7)	17 (28.3)	0.557 ^b
3–5	35 (58.3)	33 (55.0)	
>5	6 (10.0)	10 (16.7)	
Mean (SD) ^a	3.3 (1.8)	3.6 (1.8)	0.764 ^c
Body mass index(kg/m ²) ^e			0.512 ^d
18.5–24.9	10 (16.7)	9 (15.0)	
25–29.9	30 (50.0)	27 (45.0)	
More than 30	20 (33.3)	24 (40.0)	
Mean (SD) ^a	28.8 (4.2)	29.0 (4.0)	0.858 ^c
Occupation			
Housekeeper	50 (83.3)	52 (87.0)	0.894 ^b
Employed	10 (16.7)	8 (13.0)	
Marital status			
Married	50 (83.3)	55 (91.7)	0.269 ^b
Widow	9 (15.0)	5 (8.3)	
Single	1 (1.7)	0	
Regular exercise ^f	31 (51.7)	28 (46.7)	0.584 ^b
Exercise time (min)			
Mean (SD) ^a	40.0 (14/1)	41.8 (20.0)	0.491 ^c

^a Mean (standard deviation).

^b χ^2 .

^c T-Test.

^d χ^2 for trend.

^e The BMI (kg/m²) was calculated using height and weight. Based on the classifications of the World Health Organization, the values of BMI were categorized as <18.5, 18.5–24.9, 25–29.9, and ≥30.

^f Simple movements or walking at least 30 min a day.

intervention group and 36.5 months in the control group (Table 1).

The mean Greene total score was significantly lower in the Hop group than the placebo group at the end of weeks 4 (adjusted difference: -10.0, 95% confidence interval: -11.1–-8.9), 8 (-18.6, -17.1–-20.1) and 12 (-23.4, -21.6–-25.1) post-intervention. The intervention group also improved significantly in all dimensions of the Greene Scale compared with the control group.

The mean score of mental symptoms (anxiety and depression, respectively) was lower in the Hop group at the end of the weeks 4 (-1.6, -1.2–-2.0; -3.4; -2.9–-3.9), 8 (-3.4, -2.9–-3.9; -6.1, -5.5–-6.7) and 12 (-4.3, -3.7–-4.8; -7.9, -7.2–-8.6) post-intervention compared with the placebo group.

In terms of the physical symptoms score, a significant difference was observed between the intervention and control groups at the end of the weeks 4 (-2.6, -2.0–-3.1), 8 (-5.0, -4.4–-5.6) and 12 (-5.6, -5.0–-6.3) post-intervention. The mean score of vasomotor symptoms was significantly lower in the intervention group than the control group at the end of the weeks 4 (-1.9, -1.6–-2.2), 8 (-3.2, -2.9–-3.5) and 12 (-4.3, -3.9–-4.6).

A significant difference existed between the Hop and placebo groups at the end of the weeks 4 (-0.4, -0.1–-0.6), 8 (-0.7, -0.5–-0.9) and 12 (-1.2, -0.9–-1.4) post-intervention in terms of the mean sexual dysfunction score.

The number of hot flashes per week was significantly lower in

the intervention group than the control group during the weeks 4 (-8.4, -7.1–-9.8), 8 (-17.1, -14.9–-19.3) and 12 (-23.8, -21.1–-26.4) post-intervention (Table 2).

The Hop tablets had reduced the total score of the Greene Scale in premenopausal and postmenopausal women at the weeks 4, 8 and 12 post-intervention as 38%, 69.5% and 90%, respectively, compared with placebo as 1.2%, 2.6%, and 3.6%. The number of hot flashes in premenopausal and postmenopausal women at three time points was reduced in the Hop group from 35.5%, 70.5%, and 94.5%, respectively, to 1.1%, 0.4%, and 0.8% in the placebo group. No side effects were observed in the groups due to intervention.

4. Discussion

Results of the present study showed that consumption of Hop tablet dramatically reduced the mean score of the early symptoms of menopause. This decrement was quite evident according to the follow-up of the subjects for 12 weeks and comparison of the total score of the Greene Scale and its dimensions, as well as the number of hot flashes in the intervention group compared with the control group. As for our knowledge, this study is the first one which used Hop in tablet form.

The results of a randomized, double-blind study in Belgium (2006) also showed that Hop extract significantly decreased the

Table 2

The mean Greene total score and its dimensions in the treatment (Hop) and control (placebo) groups.

Outcomes	Hop (n = 60)		Placebo (n = 60)		p	Comparison Hop & placebo groups MD (95% CI) ^c
	Mean (SD) ^a	Med(per25th–75th) ^b	Mean (SD) ^a	Med (per25th–75th) ^b		
Total score Greene (0–63)						
Baseline	29.3 (9.5)	31.0 (18.0–37.7)	26.3 (8.7)	25.0 (18.2–33.7)	0.158	–3.0 (–0.2–6.2)
4 week	18.3 (7.3)	19.0 (12.0–23.7)	26.0 (8.3)	25.0 (19.0–32.0)	<0.001	–10.0 (–11.1––8.9)
8 week	8.8 (4.3)	8.5 (5.2–11.0)	25.7 (8.4)	25.5 (18.0–32.0)	<0.001	–18.6 (–20.1––17.1)
12 week	3.0 (2.0)	3.0 (1.0–4.0)	25.2 (8.0)	24.0 (18.0–31.7)	<0.001	–23.4 (–25.1––21.6)
Psychiatric symptoms (anxiety) (0–18)						
Baseline	9.6 (3.6)	10.0 (6.0–12.0)	8.7 (3.1)	8.0 (6.0–11.0)	0.313	–0.8 (–2.0–3.0)
4 week	5.8 (2.6)	6.0 (4.0–8.0)	8.6 (3.0)	9.0 (6.0–11.0)	<0.001	–3.4 (–3.9––2.9)
8 week	2.8 (1.8)	3.0 (1.2–4.0)	10.0 (2.6)	8.5 (6.0–11.0)	<0.001	–6.1 (–6.7––5.5)
12 week ^d	0.7 (1.2)	0.0 (0.0–1.0)	9.8 (2.4)	9.0 (6.0–10.0)	<0.001	–7.9 (–8.6––7.2)
Psychiatric symptoms (depression) (0–15)						
Baseline	5.7 (3.0)	5.0 (3.2–8.0)	5.2 (2.7)	5.0 (3.2–6.0)	0.129	–0.5 (–1.5–0.5)
4 week ^d	3.7 (2.2)	4.0 (2.0–5.0)	4.9 (2.6)	5.0 (4.0–6.0)	<0.001	–1.6 (–2.0––1.2)
8 week	1.9 (1.3)	2.0 (1.0–3.0)	5.0 (2.6)	5.0 (4.0–6.0)	<0.001	–3.4 (–3.9––2.9)
12 week	0.8 (0.9)	1.0 (0.0–1.0)	4.9 (2.5)	5.0 (4.0–6.0)	<0.001	–4.3 (–4.8––3.7)
Physical symptoms (0–21)						
Baseline	7.0 (3.1)	6.0 (5.0–10.0)	5.8 (3.0)	6.0 (3.0–8.0)	0.431	1.2 (–0.8–2.3)
4 week	4.1 (2.3)	4.0 (3.0–5.0)	5.6 (3.0)	6.0 (3.0–8.0)	<0.001	–2.6 (–3.1––2.0)
8 week ^d	1.3 (1.5)	1.0 (0.0–2.0)	5.4 (3.0)	5.0 (3.0–7.0)	<0.001	–5.0 (–5.6––4.4)
12 week ^d	0.2 (0.9)	0.0 (0.0–0.0)	4.4 (2.9)	5.0 (3.0–7.0)	<0.001	–5.6 (–6.3––5.0)
Vasomotor symptoms (0–6)						
Baseline ^d	4.6 (1.7)	6.0 (3.0–6.0)	4.4 (1.6)	5.0 (3.0–6.0)	0.753	–0.2 (–0.8–0.3)
4 week ^d	2.6 (1.1)	2.0 (2.0–3.7)	4.3 (1.6)	5.0 (3.0–6.0)	<0.001	–1.9 (–2.2––1.6)
8 week ^d	1.2 (0.8)	1.0 (1.0–2.0)	4.3 (1.6)	5.0 (3.0–6.0)	<0.001	–3.2 (–3.5––2.9)
12 week ^d	0.1 (0.4)	0.0 (0.0–0.0)	4.3 (1.6)	5.0 (3.0–6.0)	<0.001	–4.3 (–4.6––3.9)
Loss of interest in sex (0–3)						
Baseline ^d	2.3 (0.8)	3.0 (2.0–3.0)	2.1 (0.9)	2.0 (1.2–3.0)	0.995	–0.1 (–0.5–0.1)
4 week ^d	2.0 (0.8)	2.0 (1.2–3.0)	2.1 (0.9)	2.0 (1.2–3.0)	<0.001	–0.4 (–0.6––0.1)
8 week ^d	1.4 (0.7)	1.0 (1.0–2.0)	2.1 (0.8)	1.0 (1.0–2.0)	<0.001	–0.7 (–0.9––0.5)
12 week ^d	1.1 (0.7)	1.0 (1.0–1.0)	2.2 (0.8)	1.0 (1.0–1.0)	<0.001	–1.2 (–1.4––0.9)
Number of hot flush						
Baseline ^d	29.3 (20.5)	23.0 (14.0–36.0)	23.1 (12.3)	20.0 (14.0–28.0)	0.040	6.1 (0.0–12.2)
4 week ^d	18.9 (12.7)	16.0 (10.0–23.0)	23.1 (12.0)	21.0 (14.0–27.7)	<0.001	–8.4 (–9.8––7.1)
8 week ^d	8.8 (6.3)	8.0 (4.0–11.7)	23.2 (12.0)	21.0 (14.0–28.0)	<0.001	–17.1 (–19.3––14.9)
12 week ^d	1.4 (3.8)	0.0 (0.0–2.0)	23.2 (12.1)	20.0 (14.0–28.0)	<0.001	–23.8 (–26.4––21.1)

^a Mean (standard deviation).^b Median (percentile 25th–percentile 75th).^c Mean difference (95% confidence interval of the difference).^d This variables haven't normal distribution.

mean score of menopausal indicators and the number of hot flashes in comparison with placebo in postmenopausal women after 6 and 12 weeks ($p = 0.001$) [20]. In another trial in Finland (2010), they have used the active ingredient of hops plants as capsule. The study's participants were only 36 women in menopausal age of 45–60 years and 24 of them only received drug for 16 week, which led to reduction of vasomotor symptoms. Future extensive and more comprehensive clinical trials have been already recommended in this study [25]. In the present study we tried to provide a minimum tolerable dose with low daily frequency (once a day), appropriate drug form, and convenient use for consumer.

In recent years some prenylated chalcones present in hops have received much attention for their biological effects: for example, xanthohumol has been shown to exert cancer chemo-preventive activity in vitro experiments [26], while 8-prenylaringenin has been characterized as one of the most potent phytoestrogens isolated until now [26,27]. Hop is rich in this type of flavonoid [28]. These biological activities suggest that prenylflavonoids from hops have potential for application in cancer prevention programs and in prevention or treatment of menopausal symptoms [16].

Plant estrogens refer to nonsteroidal compounds with estrogenic activity [29]. They can be found in nearly 300 plants, including red clover, primrose, black cohosh, soy, licorice, and ginseng [30] and were used for remedy of menopausal problems, in particular hot flashes. For example, a review article stated the

reduction of hot flashes frequency by black cohosh from 7% to 34%, soy until 45%, and red clover from 1% to 56% compared with placebo [31].

Large trials have shown that although hormone therapy prevents osteoporosis and many symptoms of menopause, it increases the risk of thrombosis and breast cancer [32]. However, evidence shows that receiving high amounts of phytoestrogens is associated with reduced risk of breast cancer and not stimulation of endometrial cell proliferation [33]. When taken orally, Hop has hormonal activity [19]. Hop is used also to treat sleep disorders (through effects on the central nervous system), activation of gastrointestinal function, and as an appetizer. By the second half of the twentieth century, studies were carried out to isolate and identify its compounds for use as medicine. Estrogenic and anti-cancer properties of Hop were investigated in recent years [19,34,35]. Other beneficial effects such as reducing arthralgia, loss of appetite, reducing anxiety and nervousness, effect on kidney (diuretic), and improving sleep are also mentioned [26]; so that some participants in the intervention group in this study were noted also these beneficial effects.

According to Behre, some varieties of Hop were used in pre-historic times as brew [36]. In Rome, Hop was used as a vegetable [37]. It is now used as a flavorant in food industry [38], and due to its scented smell in creams and lotions [39]. It was also used traditionally as a mild tranquilizer [40]. Other traditional

applications of hops as stomachic, antibacterial and antifungal remedy have been shown by in vivo and/or in vitro studies [26].

Hop may cause allergic reactions in sensitive individuals. Cough and bronchial inflammation are observed in workers in the fields of Hop or those who are constantly exposed to its dust [41]. In a study on dogs, its oral chronic consumption had not any toxic reaction [42]. In the present study, no adverse event was seen.

5. Conclusion

According to the results of this study, daily consumption of Hop tablets for 4, 8, and 12 weeks had a significant effect in elimination and reduction of early postmenopausal symptoms, therefore, given the easy way of use, high acceptance of the procedure, and lack of adverse events in this study, a balanced use of this herbal remedy can be recommended in this population in order to improve the quality of life and effectiveness of women during this period.

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References

- [1] Berek J. Berek & Novak's Gynecology. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.
- [2] Speroff L, Fritz M. Clinical Gynecologic Endocrinology and Fertility. Philadelphia: Lippincott Williams & Wilkins; 2011.
- [3] Carpenter JS. The hot flash related daily interference scale: a tool for assessing the impact of hot flashes on quality of life following breast cancer. *J. Pain Symptom Manage* 2001;22:979–89.
- [4] Gold EB, Sternfeld B, Kelsey JL, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40–55 years of age. *Am. J. Epidemiol.* 2000;152:463–73.
- [5] Ghorbani M, Azhari S, Esmaili H. The relationship between life style with vasomotor symptoms in postmenopausal women referred to Women's Training Health Centers in Mashhad in 2011. *Iran J. Obstet. Gynecol. Infertil.* 2013;15:23–30 [Persian].
- [6] Mckinlay SM, Brambilla PJ, Ponsler JN. The normal menopause transition. *Maturitas* 1995;14:103–15.
- [7] NCBI. Placebo. Available at: <http://www.ncbi.nlm.nih.gov/mesh/?term=Tablet>. [retrieved 15.09.14].
- [8] World Health Organization. Women's health. Available at: <http://www.who.int/mediacentre/factsheets/fs334/en/index.html>. [retrieved 14.09.14].
- [9] Cedar M, Evans M. Danforths Obstetrics and Gynecology. London, PA: Lippincott, Williams & Wilkins; 2008.
- [10] Annese BK. Management of Perimenopausal & Post Menopausal Women. Philadelphia, PA: Lippincott; 1999.
- [11] Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *J. Am. Med. Assoc.* 2013;310:1353–68.
- [12] Ahlgrimm M. Beyond hormones other treatments for menopausal symptom. *Patient Care* 1998;28:54–7.
- [13] Forod A, Forod AD, Mahdipour S. The effects of electro-acupuncture in postmenopausal women with hot flashes. *J. Birjand. Univ. Med. Sci.* 2010;17:155–65.
- [14] Welshons WV, Murphy CS, Koch R, Calaf G, Jordan VC. Stimulation of breast cancer cells in vitro by the environmental estrogen enterolactone and the phytoestrogen equol. *Breast Cancer Res. Treat.* 1987;10:169–75.
- [15] Lobo R. Treatment of the Post Menopausal Women. Baltimore, PA: Williams & Wilkins; 1999.
- [16] Stevens JF, Page JE. Xanthohumol and related prenylflavonoids from hops and beer: to your good health. *Phytochemistry* 2004;65:1317–30.
- [17] Milligan R, Kalita JC, Heyerick A, Rong H, De cooman L, De Keukeleire D. Identification of a potent phytoestrogen in hops (*Humulus lupulus L.*) and beer. *J. Clin. Endocrinol. Metab.* 1999;84:2249.
- [18] Mckinlay SM. The normal menopause transition. *Maturitas* 1992;14:103–15.
- [19] Chadwick LR, Pauli GF, Farnsworth NR. The pharmacognosy of *Humulus lupulus L.* (hops) with an emphasis on estrogenic properties. *Phytomedicine* 2006;13:119–31.
- [20] Heyerick A, Vervarcke S, Depypere H, Bracke M, De Keukeleire D. A first prospective, randomized, double-blind, placebo-controlled study on the use of a standardized hop extract to alleviate menopausal discomforts. *Maturitas* 2006;54:164–75.
- [21] Yasui T, Yamada M, Uemura H, Ueno S, Numata S, Ohmori T, et al. Changes in circulating cytokine levels in midlife women with psychological symptoms with selective serotonin reuptake inhibitor and Japanese traditional medicine. *Maturitas* 2009;62:146–52.
- [22] Daley A, Stokes-Lampard H, MacArthur C. Exercise for vasomotor menopausal symptoms. *Cochrane Database Syst. Rev.* 2011;5:CD006108.
- [23] Anderson D, Yoshizawa T, Gollschewski S, Atogami F, Courtney M. Relationship between menopausal symptoms and menopausal status in Australian and Japanese women: preliminary analysis. *Nurs. Health Sci.* 2004;6:173–80.
- [24] Barentsen R, van de Weijer PH, van Gend S, Foekema H. Climacteric symptoms in a representative dutch population sample as measured with the greene climacteric scale. *Maturitas* 2001;38:123–8.
- [25] Erkkola R, Vervarcke S, Vansteelandt S, Rompotti P, De Keukeleire D, Heyerick A. A randomized, double-blind, placebo-controlled, cross-over pilot study on the use of a standardized hop extract to alleviate menopausal discomforts. *Phytomedicine* 2010;17:389–96.
- [26] Zanoli P, Zavatti M. Pharmacognostic and pharmacological profile of *Humulus lupulus L.* *J. Ethnopharmacol.* 2008;116:383–96.
- [27] Schaefer O, Hümpel M, Fritzeimer KH, Bohlmann R, Schleuning WD. 8-Prenyl naringenin is a potent ER α selective phytoestrogen present in hops and beer. *J. Steroid. Biochem. Mol. Biol.* 2003;84:359–60.
- [28] Milligan S, Kalita J, Pocock V, Heyerick A, De Cooman L, Rong H, et al. Oestrogenic activity of the hop phyto-oestrogen, 8-prenylnaringenin. *Reproduction* 2002;123:235–42.
- [29] Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *Air Force/Texas Coronary Atherosclerosis Prevention Study. J. Am. Med. Assoc.* 1998;279:1615–22.
- [30] Bittner V, Simon JA, Fong J, Blumenthal RS, Newby K, Stefanick ML. Correlates of high HDL cholesterol among women with coronary heart disease. *Am. Heart J.* 2000;139:288–96.
- [31] Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J. Phytoestrogens for menopausal vasomotor symptoms. *Cochrane Database Syst. Rev.* 2013;10:12. CD001395.
- [32] Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women - Principal results from the Women's Health Initiative randomized controlled trial. *J. Am. Med. Assoc.* 2002;288:321–33.
- [33] Rochira V, Faustini-Fustini M, Balestrieri A, Carani C. Estrogen replacement therapy in a man with congenital aromatase deficiency: effects of different doses of transdermal estradiol on bone mineral density and hormonal parameters. *J. Clin. Endocrinol. Metab.* 2000;85:1841–5.
- [34] Gerhauser C. Beer constituents as potential cancer chemopreventive agents. *Eur. J. Cancer* 2005;41:1941–54.
- [35] Stevens JF, Page JE. Xanthohumol and related prenylflavonoids from hops and beer: to your good health. *Phytochemistry* 2004;65:1317–30.
- [36] Wilson DG. Plant remains from the graveney boat and the early history of *Humulus lupulus L.* in W. Europe. *New Phytol.* 1975;75:627–48.
- [37] Grieve MA. Modern Herbal. New York, PA: Dover Publications Inc; 1971.
- [38] Barnes J, Anderson L, Phillipson J. Herbal Medicines: a guide for health care professionals. London, PA: Pharmaceutical Press; 2002.
- [39] Lawless J. The Illustrated Encyclopedia of Essential Oils: The Complete Guide to the Use of Oils in Aromatherapy and Herbalism. Dorset UK, PA: Element Books Ltd; 1995.
- [40] Tyler VE. The New Honest Herbal. A Sensible Guide to Herbs and Related Remedies. Philadelphia, PA: Stickley Co; 1987.
- [41] Skorska C, Mackiewicz B, Gora A, Golec M, Dutkiewicz J. Health effects of inhalation exposure to organic dust in hops farmer. *Ann. Univ. Mariae Curie Skłodowska. Med.* 2003;58:459–65.
- [42] Chappel CI, Smith SY, Chagnon M. Subchronic toxicity study of tetrahydroisohumulone and hexahydroisohumulone in the beagle dog. *Food Chem. Toxicol.* 1998;36:915–22.