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RESEARCH ARTICLE

Effects of Chicory and Fumitory on Hot Flashes of Breast Cancer Survivors Compared to Venlafaxine: A Randomized Clinical Trial

MONA MALEKZADEH MOGHANI [1], SINA MOGHTADAEI [2], ALI SONBOLI [3], SAJJAD SADEGHI [4], SEYED MOHAMMAD RIAHI [5], GHAZALEH HEYDARIRAD [2*]

[1] *Department of Radiation Oncology, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[2] *Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran, Email: dr.ghazalrad@sbmu.ac.ir*

[3] *Medicinal Plants and Drugs Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[4] *Iranian Traditional Medicine Clinic, Amiralmomenin Hospital, Semnan University of Medical Sciences, Semnan, Iran*

[5] *Cardiovascular Diseases Research Center, Department of Epidemiology and Biostatistics, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran*

**Corresponding Author*

ABSTRACT

Background and Aim: Hot flashes as an inevitable bothersome side effect of cancer therapy is an unsolved health problem in breast cancer survivors that can clearly affect quality of life of patients. The aim of this study was to compare the efficacy of distilled of chicory and fumitory as a conventional herbal remedy in Traditional Persian Medicine with venlafaxine on improving of hot flashes in breast cancer patients.

Methods: In this randomized clinical trial, participants by block randomization allocated in two groups: those who consumed distillate of chicory and fumitory (DCF), and those who took venlafaxine. The patients in two groups recorded the number and severity of hot flashes in daily diary one week before starting the intervention (baseline week). After that, they started to drink DCF (150 cc twice daily) or venlafaxine (37.5 mg in first week and 75 mg in the next three weeks) for four weeks, and accordingly completed the daily diary.

Results: 24 patients in DCF group and 17 patients in venlafaxine group completed the study. After four weeks, frequency of hot flashes in DCF group was 30.70% (p-value<0.001), and 40.88% in venlafaxine group (p-value<0.001). Also, DCF could decrease mean score of hot flashes to 41.34% (p-value<0.001), and venlafaxine could decrease to 56.93% (p-value<0.001). There were no significant differences between two groups during the first three weeks of the intervention. However, in the last week of the study, venlafaxine was more effective than DCF. As well, fewer side effects were observed in participants who received DCF.

Conclusion: DCF as well as venlafaxine could improve hot flashes score and frequency in women with breast cancer who were undergoing hormonal therapy. However, in the last week of intervention, venlafaxine was more efficient in improve hot flashes score and frequency.

KEYWORDS:
Hot flashes, breast cancer, chicory, fumitory, venlafaxine

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INTRODUCTION

Vasomotor hot flashes is one of the most common side effects of cancer treatment in breast cancer survivors [1]. Hot flashes can cause mood disorders and sleep disturbance, and clearly decrease quality of life of breast cancer patients [2, 3]. It has reported that some cancer patients even quit their standard treatments of endocrine therapy, just because of intolerable hot flashes [1].

Hot flashes characterized by episodes of sudden sensation of heating mostly in chest and face, and may repeats up to dozens of times in day and night time. The exact mechanism of hot flashes remains unclear yet. However, researchers have linked it with estrogen withdrawal and drop down of thermoregulatory center of the body in hypothalamus [4-6].

Patients undergoing breast cancer treatment usually experience hot flashes more frequent and intensive than women in normal menopause [7]. Furthermore, in breast cancer patients, there are few treatment options for hot flashes. Considering the efficacy of hormone replacement therapy (HRT) with estrogen, it is contraindicated in cancer therapy patients because of possibly increasing the risk of recurrence [6, 8]. On the other hand, there are concerns on the safety of progestational agent for management of hot flashes [6]. Besides, some conventional pharmacologic interventions for hot flashes like paroxetine and fluoxetine may interacts with tamoxifen [9]. Furthermore, non-hormonal agents including drugs belong to SSRIs and SNRIs and gabapentin have commonly numerous side effects such as xerostomia, nausea, constipation, sleep disorder, drowsiness, increasing of dizziness and worsening of fatigue that make it difficult for patients to take them in long-term [8, 10].

Unfortunately, conducted clinical trials have not led to approve a standard treatment for hot flashes of breast cancer patients. So, trying to find new effective and safe options seems to be necessary. In the last decades, hot flashes like other complications of cancer therapy have drawn a lot of attentions of researchers in the field of traditional and complementary medicine [11]. Also, patients with breast cancer in different countries widely tend to use traditional services for improving bothersome side effects of standard treatments [12]. Traditional interventions may lead to improve quality of life of cancer patients. In this regard, there are lots of papers on the evaluations of the effects of traditional and unconventional therapies including acupuncture [13], mind-body interventions [14, 15] and some herbal medicines such as soy, black cohosh and red clover on hot flashes of breast cancer patients [11]. It should be noted that some herbal agents such as soy, red clover, chaste tree and flaxseed contain phytoestrogens which are a great deal of concerns on the safety of these herbal medicine, especially in long-term in breast cancer patients [16].

In traditional Persian medicine (TPM) Cichorium intybus L. (Chicory) and Fumaria parviflora Lam. (Fumitory) are medicinal herbs that commonly have been recommended for improving hot flashes. Also, studies demonstrated some beneficial effects of them such as hepatoprotective, gastroprotective, analgesic, anti-inflammatory, antioxidant, antiallergic, antipruritic, antifeedant, antiprotozoal, antidiabetic, antimicrobial, antinociceptive and tumor-inhibitory properties of these medicinal herbs [17, 18]. As well, chemical evaluations have demonstrated little amounts of phytoestrogen in chicory and fumitory [17, 19, 20]. The aim of this study was to evaluate the efficacy and safety of DCF compare with venlafaxine as a routine pharmacologic medicine on hot flashes of breast cancer survivors undergoing hormonal therapy.

MATERIAL AND METHOD

Trial design

We designed a randomized, open-label, parallel, active-controlled trial. In this trial, we evaluated the safety and efficacy of DCF in management of hormonal therapy induced hot flashes in breast cancer patients. This clinical trial generally was founded based on similar studies especially Loprinzi CL, et. al (1994) [21]. No changes occurred in the methods after trial commencement.

Participants

The inclusion criteria of this study were: women with breast cancer (stage 0-3) older than 18 years who had hot flashes at least two weeks before trial, completing the treatment such as chemotherapy, radiotherapy, and surgery, starting hormone therapy including tamoxifen, LHRH agonists, and aromatase inhibitors more than four weeks before the study, not taking anti-depressant agents including SSRIs and SNRIs as well as hormonal drugs and phytoestrogens in recent two weeks before the study, having normal BUN, Cr and Bilirubin in accordance with reference range of laboratory, and having at least two episodes of hot flashes daily and 14 a weekly. All participants signed the informed consent form to enroll in the study. The exclusion criteria were metastasis or having another malignancy at the same time, taking anti-depressant drugs during five weeks of study, alteration in hormone therapy plan for breast cancer within five weeks after starting the trial, to be undergoing chemotherapy/radiotherapy, the patient's desire to withdraw from the study, and known allergy to venlafaxine, chicory and fumitory.

Intervention

Women with breast cancer having hot flashes were referred to the researcher by the oncologist, then eligible patients were divided into two parallel groups. participants were randomly assigned to receive combination of DCF 150 cc either 4 weeks (twice daily) as the intervention group, or venlafaxine 37.5 mg in the first week and 75 mg in the next three weeks, as the control group.

Outcomes

The number and score of hot were set as the primary outcome measure. Participants were asked to fill daily diaries of hot flashes a week before intervention as the baseline which the number and score of hot flashes in the rest of the study were compared with that. That is a valid daily dairy among researchers which have used in different studies [21, 22] In that diary, the number and intensity of hot flashes were recorded as mild, moderate, severe or very severe (According to guideline). Accordingly, the number and score of hot flashes (number × intensity degree: 1-4 respectively) were considered. Any reported adverse event was also measured as the secondary outcome. No changes were made to the trial outcomes after the trial commenced.

Safty assessment

All the participants were followed by the investigator every 2 weeks with the aim of distinguishing the possible side effects of the drug. All the participants were requested to inform any side effects of the drug. Also, the phone number of the researcher was available for all participates.

Sample size

Based on the expected score of hot flashes, as one of the outcome measures, between the two groups of the trial according to a previous study and by taking into account two-sided significance level of 0.05 and power of 90%, the sample size was calculated 24 patients in each group. Considering the possibility of failure to follow up and patients' drop out, in order to increase the power of the study, the sample size was calculated 26 patients in each group to be totally 52 patients.

Randomization

Convenience sampling was done from all patients with hot flashes referring to cancer clinic of Shohadaye Tajrish hospital (Tehran, Iran). Fifty-two eligible patients were randomized in two parallel groups. A statistician generated a randomized list by using a statistical software, via simple block randomization method. Then, the eligible patients were assigned into two groups by a researcher according to the randomized list.

Ethical issues

The trial was in compliance with the Declaration of Helsinki and also reviewed, approved, and monitored by the ethics committee of Shahid Beheshti University of Medical Sciences (Licensenumber: IR.SBMU.RETECH.REC.1396.448). All the participants signed an informed consent form prior to their enrollment in the study.

Statistical methods

All data were described by mean ± standard deviation or number. Mann–Whitney U tests were used for statistical comparison of baseline characteristics. The Wilcoxon signed-rank test was used to determine the changes in outcomes between the two groups of the study. P values less than 0.05 were considered significant. All the data were analyzed using Statistical Package for the Social Sciences software, version 15 (SPSS Inc., Chicago, IL, USA).

Plant material

Aerial parts of dried chicory and fumitory which collected from South Khorasan Province of Iran in form of sorted materials were purchased from a valid herbal medicinal market in Tehran Province of Iran .Voucher specimens of the verified plant samples (MPH-2762 for chicory and MPH-2763 for fumitory) were deposited in the Herbarium of Medicinal Plants and Drugs Research Institute (MPDRI) of Shahid Beheshti University (Tehran, Iran).

Preparation of distillate

Hydrodistillation technique was used for preparation of distillate of chicory and fumitory. Air dried aerial parts of the plants (20 kg) were subjected for distillation using 300 L distilled water at 120 C for 3 h. The obtained distillate of the plants (1:5) were filtered and stored in the sealed pet containers until tests and analysis at ambient temperature.

Quality control of distillates

Standardization of distillate of chicory and fumitory was performed by isolation of volatile compounds through liquid-liquid extraction using ethyl acetate as solvent and analyzed by GC-MS method [23].

RESULTS

Phytochemical analysis and microbial assay

Phytochemical analysis of DCF resulted in the identification of three major components (Figure 1, Table 1). Spathulenol with 41.3% was found to be the principal constituent followed by dihydroactinidiolide (8.4%) and anisyl methyl ketone (3.3%).

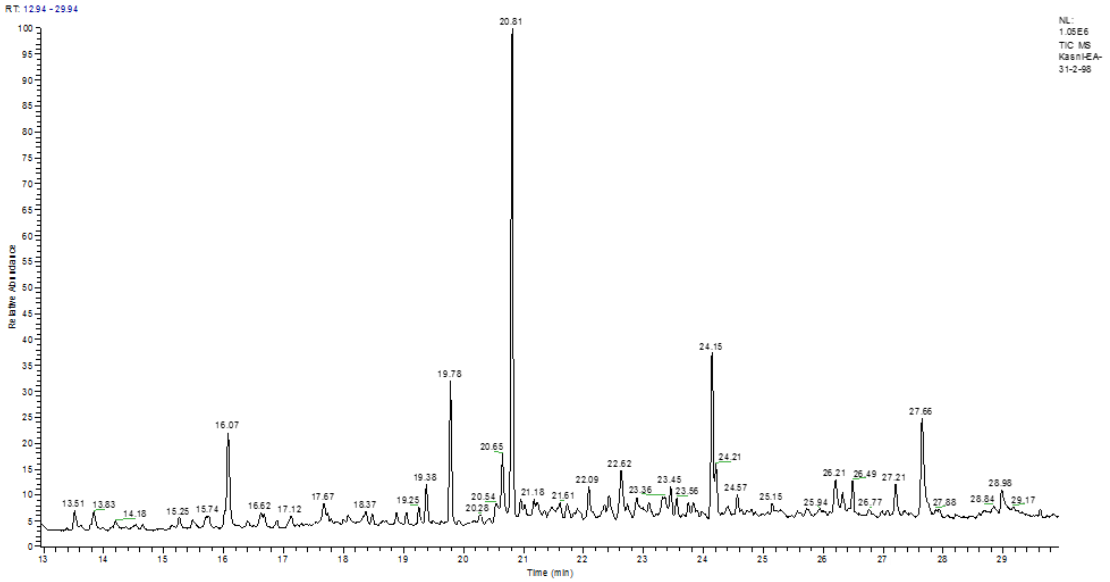

Fig.1: GC-MS chromatogram of extract from liqid-liqid distillate of chicory with ethyl acetate as solvent

Table 1: Major components of distillate of chicory

Compound	Retention time	Retention index	GC-FID * (%)
Anisyl methyl ketone	16.07	1389	3.3
Dihydroactinidiolide	19.78	1538	8.4
Spathulenol	20.81	1581	41.3

* Gas Chromatography-Flame Ionization Detector

Assay of distillates for microbial contamination revealed that TAMC (<10 cfu/mL) and TYMC (<10 cfu/mL) were within normal ranges according to acceptable criteria of United States Pharmacopeia [24]. Also, the two samples were negative with respect to existence of Escherichia coli and Salmonella typhi. The results confirmed the safety of distillates for further clinical usage.

Participants' enrollment

In this clinical trial, 83 patients with hot flashes were referred to the researcher, and eligible subjects (N=52) allocated in distilled Chicory and Fumitory group (N=27) and Venlafaxine group (N=25). Finally, 24 participants in chicory and fumitory group and 17 subjects in venlafaxine group completed the trial (fig.2)

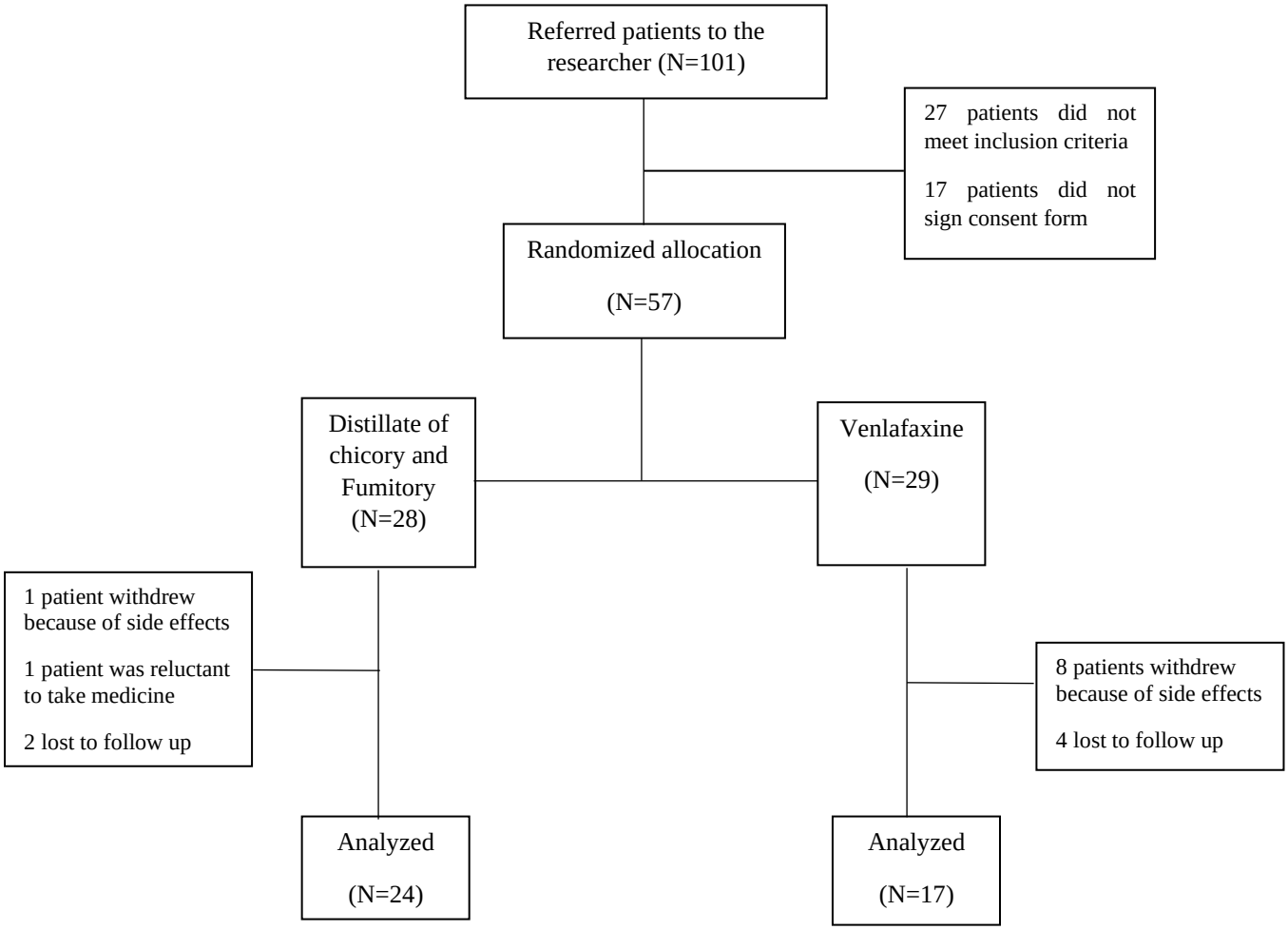

Fig.2: Flow diagram of the groups' allocation, enrolment, intervention, follow-up, and the analysis in both groups of the study

Basic characteristic

Characteristics of the patients in two groups are listed in Table 2. As can be seen, all baseline characteristics of the subjects in two groups were similar (P value > 0.05).

Table 2: Charectristics of the subjects of the trial

	DCF*		**Venlafaxine**		
Characteristic	NO.	%	NO.	%	P value
Total No. of patients	24	100	17	100	
Age (years; mean [SD])	46.66 (7.428)		44.82 (7.460)		0.439
BMI (kg/m2; mean [SD])	26.24 (2.752)		27.52 (2.788)		0.151
Stage of cancer: Stage 1 Stage 2 Stage 3	 12 9 3	 50.0 37.5 12.5	 10 6 1	 58.8 35.3 5.9	 0.488
Type of endocrine therapy: Tamoxifen Aromatase inhibitors	 16 8	 66.7 33.3	 13 4	 76.5 23.5	 0.729
Menopause status: Yes No	 21 3	 87.5 12.5	 15 2	 88.2 11.8	 > 0.999
Smoking Yes No	 0 24	 0 100	 0 17	 0 100	 -

*DCF: distillate of chicory and fumitory

The mean daily number of hot flashes of DFC and venlafaxine groups subjects in the baseline week were 9.14 and 9.06 respectively. Also, baseline's hot flashes score in DCF and venlafaxine groups were 18.33 and 17.71 respectively. The

status of hot flashes of the subjects are shown in Table 3. It should be pointed that baseline status in two groups were not different statistically (P value > 0.05).

Table 3: Hot flashes status of the subjects

Characteristic	DCF*	Venlafaxine	P value
Mean daily number of hot flashes (mean [SD])	9.14 (2.194)	9.06 (2.347)	0.534
Mean daily hot flashes score (mean [SD])	18.33 (5.976)	17.71 (5.553)	0.738

*DCF: distillate of chicory and fumitory

Clinical response

Table 4 shows a full description of the mean daily number of hot flashes, weekly in each group. A significant improvement was observed in the mean daily number of hot flashes in the both groups (p-value<0.001). The mean of daily number of hot flashes decreased 30.70% in DCF group, and 40.88% in venlafaxine group.

Table 4: Status of hot flashes score in five weeks of the study

Study weeks	Treatment groups	Mean daily number of hot flashes	Std. Deviation
Week 1 (Baseline)	DCF*	9.1488	2.19400
	Venlafaxine	9.0672	2.34745
Week 2	DCF	6.7857	1.60246
	Venlafaxine	7.0672	1.59169
Week 3	DCF	6.2560	1.62281
	Venlafaxine	5.9664	1.26826
Week 4	DCF	6.4762	1.95679
	Venlafaxine	5.8403	1.26661
Week 5	DCF	6.3393	1.77172
	Venlafaxine	5.3613	.98083

*DCF: distillate of chicory and fumitory

By comparison of the mean differences between the groups, no significant differences were observed in the mean daily number of hot flashes on the first three weeks of the intervention (P value > 0.05). However, in the last week of the study venlafaxine could decrease the number of daily hot flashes significantly more than DCF (p-value =.046) (Fig.**3**).

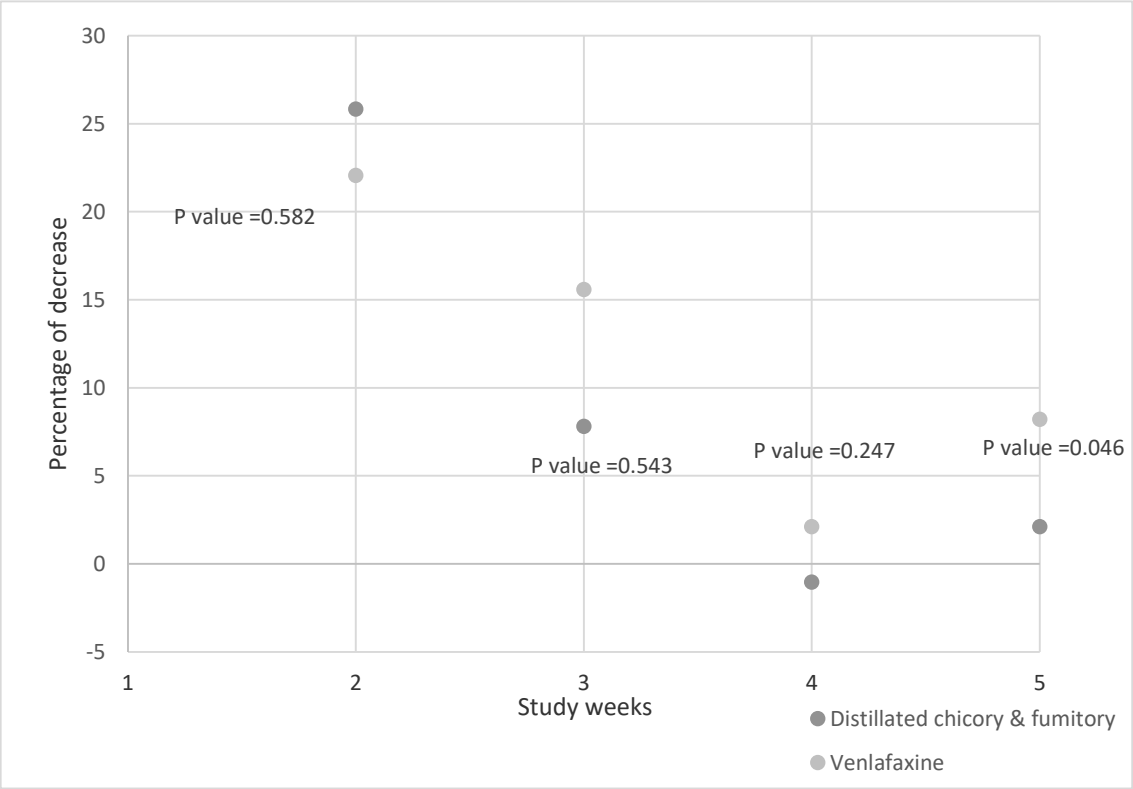

Fig.3: Comparison of the percentage of decrease in number of hot flashses in two groups during four weeks of interventions. P value within two groups were shown.

There was also significant improvement in the mean score of hot flashes in the both groups (p-value<0.001). The mean score of hot flashes were 41.34 and 56.93 respectively. Table 5 shows a full description of the mean score of hot flashes, weekly in each group.

Table 5: Status of hot flashes score in five weeks of the study

Study weeks	Treatment groups	Mean daily score of hot flashes	Std. Deviation
Week 1 (Baseline)	DCF*	18.3333	5.97669
	Venlafaxine	17.7143	5.55354
Week 2	DCF	11.7560	3.65468
	Venlafaxine	12.9580	4.41379
Week 3	DCF	10.6369	4.19553
	Venlafaxine	9.2941	2.72108
Week 4	DCF	10.2262	4.03510
	Venlafaxine	8.7059	2.46582
Week 5	DCF	10.7560	3.67670
	Venlafaxine	7.6303	1.83507

*DCF: distillate of chicory and fumitory

By comparison of the mean differences between the groups, no significant differences were observed in the mean score of hot flashes on the first three weeks of the intervention (P value > 0.05). However, in the last week of the study venlafaxine could decrease the mean score hot flashes significantly more than DCF (p-value=0.003) (Fig.4).

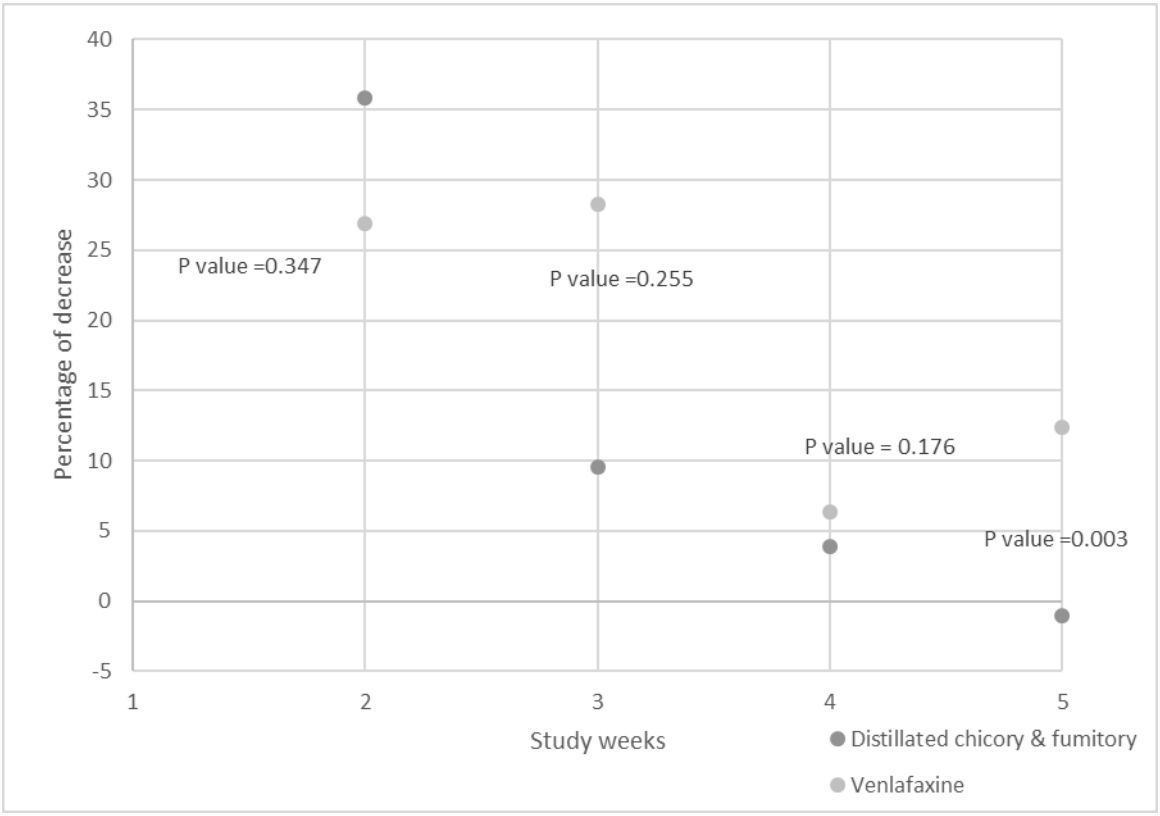

Fig.4: Comparison of the percentage of decrease in score of hot flashses in two groups during four weeks of interventions. P value within two groups were shown**.**

Harms

In this clinical trial, 4 patients in DCF group, and 10 patients in venlafaxine group reported side effects. Table **6** reveals side effects in the two groups.

In DCF group, only one patient was withdrawn from the study due to severe abdominal bloating. While, 8 patients of venlafaxine group could not tolerate venlafaxine and did not complete the study.

Table 6: Side effects of two interventions in this trial

Study groups	Side effects	Number of cases	Results of follow up
Distillate of chicory-fumitory (DCF)	Chill in two cases	2	Decreased in severity over time
	Intensify of tingling paresthesia	1	Decreased in severity over time
	Abdominal bloating	1	It led to exit the patient from the study.
Venlafaxine	Nausea	6	Generally occurred in the first week of intervention, it was intolerable for participants, and led to withdraw from trial.
	Constipation	2	The severity was mild and resolved over time.
	Dry mouth	1	Decreased in severity over time
	Headache	2	One case was severe, and three cases were mild in the first week. All resolved after cessation of venlafaxine.
	Dizziness	2	Improved over time
	Mood disturbances	3	Increasing anxiety in one case and unpleasant feeling in two cases
	Sleep disturbances	2	One case had mild insomnia, another one got over sleepiness. All two effects improved over time.

DISCUSSION

Hot flashes are reported by the most of breast cancer survivors and their quality of life was adversely affected. Concerning that in breast cancer survivors, estrogen exposure increases cancer recurrence rates, hormonal therapy is not the recommended as a first-line treatment of hot flash for breast cancer survivors.

In the last decades, herbal medicines have become a notable subject of interest for the researchers in field of hot flashes of both prostate and breast cancer patients, and many related clinical studies have been conducted [25]. Many clinical trials have been conducted to evaluate efficacy of

herbal and natural products in the treatments of hot flashes of breast cancer survivors [26-28]. Although studies have suggested that some medicinal herbs are effective in management of hot flashes [29-32], but considering phytoestrogen contents of those herbal agents such as soy, red clover, chaste tree and flaxseed, they are not proposed as safe interventions for breast cancer survivors [16]. Considering little amount of phytoestrogen components in chicory and fumitory, it seems they are beneficial herbs for breast cancer survivors who have undergoing hormone therapy. In this study, the efficacy of the DCF in the management of hot flashes in breast cancer survivors compared to venlafaxine was evaluated via a randomized clinical trial. Results of the study showed DCF could improve hot flashes as well as venlafaxine, however, in the last week of intervention, venlafaxine was significantly more effective. It should be noted that although venlafaxine was more effective in managing hot flashes in the last week of the intervention, but it was difficult for patients to tolerate it and a few participants withdrew the study due to various side effects, especially in the first week of the intervention (Table 7).

There are a lot of papers about efficacy of venlafaxine for management of hot flashes in cancer treatment centers. Studies indicate that venlafaxine 75 mg daily is effective on improvement of hot flashes ranged from 25 % to 61% in different clinical trials [33-35]. In Loprinzi et. al study [34] venlafaxine decreased the number of hot flashes as well as the mean score of hot flashes 46% and 61% , respectively. Results of our study showed venlafaxine decreased 40.88% number of hot flashes and 56.93% the mean score of hot flashes.in this regard, results of this study is similar to Loprinzi et. al study.

In our study, DCF decreased significantly the number of hot flashes (30.70%), and the mean score of hot flashes (41.34%).

In Eleanor et. al study, as a similar study, there was no significant difference between acupuncture and venlafaxine on improvement of hot flashes, also, in their study the efficacy of acupuncture and venlafaxine in a 12-weeks trial was less than our study [35].

Johns et. al via a systematic review compared different pharmacological treatments such as citalopram, venlafaxine, gabapentin, and paroxetine; and they mentioned that use of venlafaxine could reduce hot flash symptoms very fast, and participants preferred venlafaxine over gabapentin and clonidine. Although venlafaxine was associated with increased gastrointestinal side effects such as xerostomia, nausea, and constipation, but it has suggested as a reasonable first medication for management of hot flashes [8]. A comparison of side effects between the two groups in our study showed that DCF not only had fewer side effects than venlafaxine, but also, participants were more inclined to use this natural remedy.

This becomes even more important regard to the numerous side effects of pharmacological treatments such as venlafaxine which limit long-term use of this medications [34-36]. Although Johns et. al study mentioned that dropout rate of these pharmacological treatments was less than 20 % and suggesting good tolerability of these treatments [8], but results of our study showed that many participants did not tolerate venlafaxine, especially at the beginning of the treatment, and the dropout rate was more than 32%. In this regard, Eleanor et.al concluded that "Many women refuse this approach because of the potential adverse effects or because they do not want any more medication" [35]. So, use of DCF as a natural medicine seems to be useful on improvement of hot flashes in patients who do not willing to take chemical drugs or could not tolerate venlafaxine.

Study limitations

Some limitations of this study are supposed to be considered for achieving a comprehensive and reliable conclusion about final results. The small sample size should be stated as a major regard. However, in this study we planned to evaluate our hypothesis in a standard minimum sample size. Lack of multiple dose evaluation or an intervention dose adjustment in our study is yet one more issue, which should be considered in future studies. Also, this study was an open-label study which is faced with the constraint of open-label studies with related bias.

Registration

This study was approved by local committee of medical ethics, Shahid Beheshti University of Medical Science (approval code: IR.SBMU.RETECH.REC.1397 .827), which registered in Iranian Registry of Clinical Trials (registration code: IRCT20190107042275N1).

CONCLUSION

According to the results of this preliminary study, DCF as well as venlafaxine could improve hot flashes score and frequency in women with breast cancer who were undergoing hormonal therapy. However, in the last week of intervention, venlafaxine was more efficient in improve hot flashes score and frequency. Further clinical trials with larger sample size and long- term follow up are recommended to confirm the efficacy of DCF on hot flashes of cancer survivors.

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CONFLICT OF INTEREST

The authors had no conflicts of interest to reveal.

Ethical Standards

The authors declare that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008.

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