Research Journal of Pharmacognosy (RJP) 10(4), 2023: 17–29
Received: 18 May 2023
Final revision: 7 Aug 2023
Accepted: 21 Aug 2023
Published online: 30 Aug 2023
DOI: 10.22127/RJP.2023.396666.2119

Original article

Effects of Chicory-Fumitory Syrup on Hot Flashes in Comparison with Megestrol in Prostate Cancer Patients: a Randomized Controlled Clinical Trial

Sajjad Sadeghi[1], Farzaneh Ghaffari[1], Bahram Mofid[2], Mozhgan Mehri Ardestani[3], Ghazaleh Heydarirad[1*]

[1]Traditional Medicine and Materia Medica Research Center and Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[2]Department of Clinical Oncology, Shohada-e-Tajrish Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[3]Department of Persian Medicine, Faculty of Medicine, AJA University of Medical Sciences, Tehran, Iran.

Abstract

Background and objectives: Hot flashes are among the common and bothersome side effects of androgen deprivation therapy (ADT) in men with prostate cancer. Given the lack of standard treatment, further research is required to develop efficient and safe treatments. **Methods:** In the present randomized controlled clinical trial, patients with prostate cancer undergoing ADT were randomly allocated into chicory-fumitory syrup (from hydroalcoholic extract of chicory and fumitory) and megestrol groups. The participants recorded the number and severity of hot flashes in a daily diary one week before the intervention (baseline). Next, they started the syrup (5 mL twice daily) and megestrol (20 mg twice daily) for four weeks and completed the diary. **Results:** A total of 69 patients completed the study (35 patients in the chicory-fumitory group and 34 patients in the megestrol group). After four weeks of the intervention, the mean daily frequency of hot flashes in the chicory-fumitory group decreased to 38.19% (p=0.004); the hot flash score also decreased to 44.39% (p=0.008). In the megestrol group, the mean frequency of hot flashes was decreased by 68.93% (p<0.001), and the mean hot flash score was reduced by 67.47 (p=0.001). According to the independent samples t-test, the number and severity of hot flashes showed a more significant reduction in the megestrol group compared with the chicory-fumitory group (p=0.001 and p=0.021, respectively). **Conclusion:** The chicory-fumitory syrup is effective against hot flashes in men with prostate cancer; however, the reduction in the number and severity of hot flashes in the megestrol group was more prominent. Further clinical trials with longer intervention periods, and larger sample sizes are recommended to confirm the efficacy of chicory and fumitory against hot flashes.

Keywords: chicory; fumitory; hot flashes; megestrol; prostate cancer; Iranian traditional medicine

Citation: Sadeghi S, Ghaffari F, Mofid B, Mehri Ardestani M, Heydarirad Gh. Effects of chicory-fumitory syrup on hot flashes in comparison with megestrol in prostate cancer patients: a randomized controlled clinical trial. Res J Pharmacogn. 2023; 10(4): 17–29.

Introduction

Hot flash, a common side effect of androgen deprivation therapy (ADT), the essential treatment of advanced-stage prostate cancer, is annoying and sometimes intolerable [1,2]. It negatively impacts the quality of life of men with prostate cancer [3], may disturb their sleep [4],

*Corresponding author: dr.ghazalrad@sbmu.ac.ir

affects their mood and social relationship [5], and causes psychological distress [6]; even some patients may discontinue their treatment because of this tormenting and incapacitating situation [2]. Hot flashes manifest with periods of sudden sensation of heating, sweating, and flushing ranging from a few seconds to one hour [7]. These episodes can be repeatable and accomplished by nausea, irritability, and anxiety [8]. It should be noted that hot flashes usually are a long-lasting side effect of ADT, which may persist with the same severity and duration even after cessation of ADT [2,9]. The possible mechanism of hot flashes due to ADT is mainly related to the instability of the hypothalamus's thermoregulatory center because of changing levels of sex steroid hormones. These changes are thought to lead to changes in brain neurotransmitters and disturb the normal function of the thermoregulatory system [10].

In the last decades, many clinical studies have been conducted on the effects of pharmacologic interventions in hot flashes of men with prostate cancer. The efficacy and toxicity of some hormonal agents, including diethylstilbestrol, cyproterone acetate, medroxyprogesterone acetate, megestrol acetate, estetrol, and some other drugs such as combined phenobarbital plus ergotamine, gabapentin, clonidine, venlafaxine, and paroxetine have been evaluated. However, the results of some studies were not satisfying, and multiple side effects including weight gain, fatigue, dyspnea, enlarged breasts, and even rise in prostate-specific antigen (PSA) have been reported [1,11-14]. Among these drugs, some researchers suggested the efficacy of megestrol in alleviating hot flashes in prostate cancer survivors [13,15]. However, experts generally have no agreement on a standard drug for treating hot flashes due to insufficient studies on the efficacy and safety of the pharmacological interventions [16].

Traditional and complementary medicine (TCM) has been one of the research interests of researchers in hot flashes. Some studies have investigated the efficacy of acupuncture, cognitive behavioral therapy, and herbal medicine such as soy, flaxseed, and sage on hot flashes [1,17,18].

Cichorium intibus L (chicory) and *Fumaria parviflora* Lam. (fumitory) are medicinal herbs that have been used in Persian medicine since ancient times [19,20]. Studies provided evidence of antioxidant, anti-inflammatory, analgesic, antiallergic, hepatoprotective, gastroprotective, antipruritic, antifeedant, antiprotozoal, antidiabetic, antimicrobial, antinociceptive and tumor-inhibitory properties of these two herbal medicines [20,21]. Chicory not only contains nutrient substances such as fats, proteins, minerals and vitamins, but it is also rich in bioactive components including inulin, sesquiterpene lactones, flavonoids, alkaloids, steroids, terpenoids, β-carotene, zeaxanthin, hydroxycoumarins, caffeic acid derivatives, steroids, terpenoids, and volatile compounds [22]. Also, fumarine, protopine, caffeic acid, parfumine, oxyberberine, protocatechuic, cryptopine, berberine, sesquterpenoids are known biological ingredients of fumitory [20].

From the perspective of Persian medicine, chicory is a plant with cold-wet temperament with many benefits including thirst-relieving, reducing "Safra" (yellow bile), improving stomach inflammation, removing liver blockages, decreasing liver heat and purifying blood. Chicory has also benefits for the urinary and kidney systems and is useful in some kind of headaches [23,24]. Besides, fumitory is described as a plant with moderate-dry temperament which is useful for disorders of stomach, liver, spleen, mouth and skin [24].

Persian medicine resources propose chicory and fumitory for managing diseases related to heat and flushing, such as fever, hyperthermia, and hot flashes [24]. Furthermore, chicory and fumitory have been used traditionally by people for treatment of hot flashes [25]. Recently published clinical trials have demonstrated chicory and fumitory's efficacy in alleviating hot flashes of women surviving breast cancer [26,27]. Nevertheless, no study has been published on the efficacy of these herbal medicines in hot flashes of men with prostate cancer. Thus, the present controlled clinical trial was aimed to evaluate the effects of a traditional herbal product derived from chicory and fumitory compared to a conventional drug (megestrol) on hot flashes in prostate cancer patients undergoing ADT.

Material and Methods

Ethical considerations

This randomized controlled clinical trial was approved by the local ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (approval code:

IR.SBMU.RETECH.REC.1397.826), and followed the declaration of Helsinki. Written informed consent was obtained from all participants of the study. Also, the clinical trial was registered at the Iranian registry of clinical trials (registration code: IRCT20190112042333N1).

Plant material

The dried aerial parts of chicory (*Cichorium intybus* L.) and fumitory (*Fumaria parviflora* Lam.) were purchased from a herbal medicine store in Tehran (2017), and then authenticated by a botanist at the Herbarium of the Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. The specimens were deposited at the herbarium of Tehran University of Medical Sciences under the voucher number of MPH-2762 for chicory and MPH-2763 for fumitory.

Preparation

The traditional product of the present study comprised of hydroalcoholic chicory and fumitory extracts. To prepare the herbal product, chicory and fumitory were cleaned and washed from dust and possible waste materials. After drying and grinding, the plant was extracted by macerating with 70% ethanol. Then, the extract was concentrated by rotary, and dried with the help of a freeze dryer. Finally, 36 grams of dried extract from chicory and 18 grams of dried extract from fumitory were dissolved in 120 mL of 70% (w/w) sugar solution in distilled water and then mixed. Each 5 mL of syrup contained 1.5 g of dried extract of chicory and 0.75 g of dried extract of fumitory.

The resulting solution was placed in 240 mL dark plastic bottles with labels, and then stored in a dry, cool and dark place.

Microbial and fungal tests of the product were carried out by determining the total aerobic microbial count (TAMC) and total combined yeast and mold count (TYMC). Also, the samples were tested for *Escherichia coli* and *Salmonella* spp, according to the acceptance criteria of the United States Pharmacopeia [28].

Total phenolics content

For product standardization, the total phenolic content, was determined as a marker using the spectrophotometric method following standard procedure based on the Folin–Ciocalteu method [29].

Study design

This randomized controlled clinical trial was conducted in the oncology clinic of Shahid Labbafinejad Medical Center in Tehran, Iran, between January 2018 and September 2019. This study was designed based on the method proposed by Loprinzi CL et al. in 1994 [15], which has been used in several studies to evaluate hot flashes in prostate and breast cancer patients [30-32]. The study was conducted over five weeks, consisting of one baseline week and four intervention weeks. In the baseline week, the participants only recorded the number and severity of daily hot flashes in their daily diary [33]. After the baseline week, the patients were asked to use their medications and record the number and severity of hot flashes within four weeks.

This clinical study had two parallel arms: chicory-fumitory syrup and megestrol. After baseline week, based on the simple randomization method in a randomizer software tool (Random Rx Ver.1), eligible subjects were allocated into two groups. Subjects in experimental group received 5 mL of the syrup containing extracts of chicory-fumitory syrup twice a day; while subjects in control group received 20 mg of megestrol twice a day for four weeks.

Study population

Prostate cancer patients with hot flashes undergoing androgen deprivation therapy (ADT) were referred to the researcher by the urooncologist. After the researcher evaluated the inclusion criteria, eligible patients were asked to sign the written informed consent form if they were willing to participate in the study.

Inclusion criteria

(1) Undergoing ADT more than eight weeks before the trial; (2) having hot flashes at least four weeks before the trial; (3) having at least two episodes of hot flashes daily.

Exclusion criteria

Patients undergoing chemotherapy/radiotherapy, patients taking antidepressants (e.g., SSRIs) in the past four weeks, and patients with advanced kidney, liver, coagulation, or vascular disorders were excluded.

The patients were explained that they could withdraw from the study for any reason at any time. Also, they were asked to report any new

symptoms or serious and bothersome side effects during the study.

Outcome measures

Two outcomes of this study included the mean daily number of hot flashes and the mean daily score of hot flashes. The mean number of hot flashes could be calculated directly based on the daily hot flash diary, and the score of daily hot flashes was calculated as follows:

Score = Number of mild hot flashes × 1 + Number of moderate hot flashes × 2 + Number of severe hot flashes × 3 + Number of very severe hot flashes × 4

It should be noted that the severity of hot flashes was determined by the patients based on their diary guide [33]. This 4-category hot flash diary was developed by Sloan et al. [34] and was used as a valid tool in further studies. Complete written explanations of differentiation of hot flashes severity along with daily diaries were provided to the patients.

For both variables, the daily average of the last week of intervention was compared with the baseline week for each patient. Also, at the end of the study, the participants were asked about their satisfaction with the intervention based on a 5-point Likert scale ranging from one ("not satisfied") to five ("very satisfied").

Safety assessment

The dosage of the syrup was determined according to recent research and the recommended dosages of chicory and fumitory [35-37]. The dose of megestrol was also determined based on similar studies [13,15,38]. All participants were followed up regarding any possible adverse events or toxicity during the trial and were free to contact the researcher.

Sample size

Based on a similar study [15], by assuming a 50% decrease in the frequency of hot flashes at an alpha level of 5%, power (1–β) of 0.80, standard deviation (SD) of 6.3, and an attrition rate of 10% during the study, the final sample size was calculated by the methodologist as 35 subjects per group. This sample size was calculated to identify a difference of 4.5 in the average number of hot flashes due to a 50% decrease in the score of hot flashes.

Statistical analysis

This study compared quantitative variables before and after the intervention, using Wilcoxon or paired t-tests. Also, the Chi-square test was used to compare qualitative variables. Repeated measures analysis of variance was used to compare the two groups in the measurements. The normality hypothesis was tested using the Shapiro-Wilk test, and a significance level of 0.05 was considered. The data was extracted from the forms and analyzed in SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results and Discussion

The amount of total phenolic contents of the syrup was found to be 5.18±0.148 mg of gallic acid equivalent (GAE) per one mL of the syrup. All the results were within the normal range

In this trial, a total of 201 patients referred by an oncologist were enrolled in this study. Of these patients, 117 men were eligible for the trial and were allocated to two groups by randomization: megestrol (n=61) and chicory-fumitory syrup syrup (n=56). Finally, the data of 69 participants (34 participants in the megestrol arm and 35 participants in the chicory-fumitory syrup arm) were analyzed (Figure 1).

The mean age of the subjects was 67.4 years (67.11 years in the chicory-fumitory syrup group and 66.97 years in the megestrol group). Most of the participants were retired with an education level under diploma. The demographic characteristics of the participants in the trial are shown in Table 1. According to Chi-square and Fisher's exact test results, the characteristics of the patients in the two groups were not significantly different ($p>0.05$). Also, about half of the participants had a history of hot flashes over nine months. The history of ADT therapy before the study was 14.21 months in the chicory-fumitory syrup group and 13.52 months in the megestrol group. The median number of daily hot flashes in the baseline week was 8.10 in the chicory-fumitory syrup group and 7.49 in the megestrol group. Besides, the mean score of daily hot flashes before the intervention was 13.46 in the chicory-fumitory syrup group and 11.28 in the megestrol group. The two groups were similar regarding hot flash frequency, score, and other related characteristics before the intervention ($p>0.05$) (Table 2).

The severity of hot flashes was mild to moderate in most patients of the two groups (65.7% in the chicory-fumitory syrup group and 79.4% in the megestrol group) in the baseline week (Figure 2).

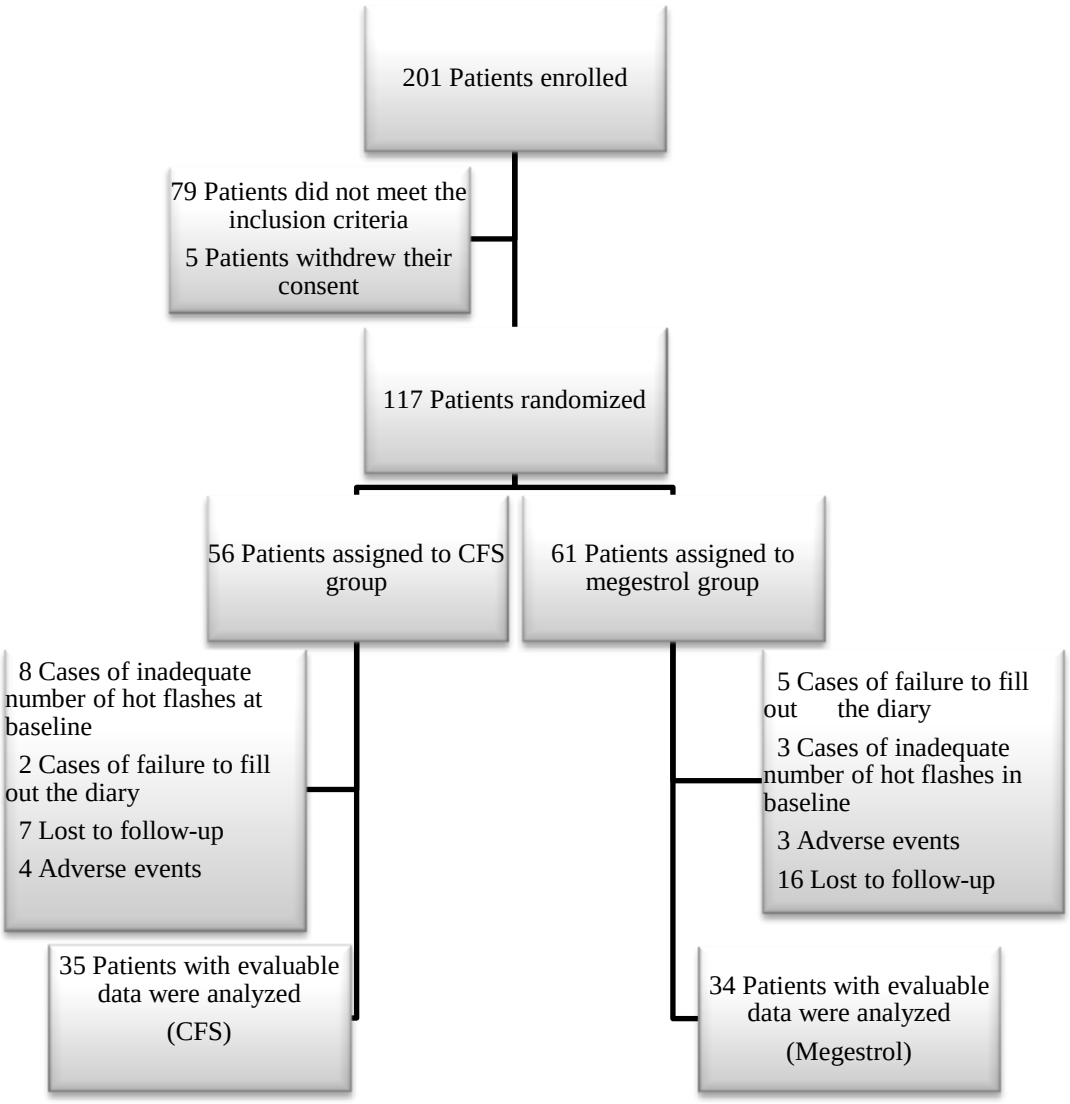

Figure 1. Consort flow chart of the trial; CFS: chicory-fumitory syrup

Table 1. Characteristics of the participants

	Chicory-fumitory syrup		Megestrol		
Characteristics	**No.**	**%**	**No.**	**%**	**p value**
Age (years; mean [SD])	67.11 (8.415)		66.97 (8.701)		0.945
BMI (kg/m^2; mean [SD])	27.32 (4.19404)		26.49 (3.67795)		0.403
Education					
Elementary	8	25	9	29	0.978
Under diploma	20	62.5	15	48.4	
Graduate	4	12.5	7	22.6	
Occupation					
Working	10	30.3	10	31.3	0.934
Retired	23	69.7	22	68.7	
Type of ADT					
Hormone therapy	32	95	31	94	1.000
Orchiectomy	2	5	2	6	
Smoking					
Yes	4	13.3	4	14.3	1.000
No	26	86.7	24	85.7	
Drug abuse					
Yes	2	10.5	3	30	0.306
No	17	89.5	7	70	
History of radical prostatectomy					
Yes	26	86.7	16	66.7	0.079
No	4	13.3	8	33.3	
History of chemotherapy					
Yes	3	9.1	5	17.2	0.456
No	30	90.9	24	82.8	
History of radiotherapy					
Yes	18	56.3	15	55.6	0.957
No	14	43.7	12	44.4	

Table 2. Status of hot flashes in the two groups before the intervention

Characteristics	**Chicory-fumitory syrup**		**Megestrol**		
	NO.	**%**	**NO.**	**%**	**p value**
Duration of hot flashes					
9 mo. ≥	17	50	17	51.5	0.901
9 mo. <	17	50	16	48.5	
Estimated number of daily hot flashes before the study					
1-3	9	39.1	7	36.8	0.598
4-9	11	47.8	10	52.6	
10 ≤	3	13	2	10.5	
Mean estimated number of daily hot flashes before study; mean (SD)	5.30 (4.084)		4.79 (2.446)		0.598
Number of daily hot flashes; mean (SD)	8.10 (6.00)		7.49 (6.11)		0.676
Daily hot flashes score; mean (SD)	13.46 (13.26)		11.28 (13.08)		0.494

After four weeks of using the chicory-fumitory syrup, the mean daily number of hot flashes significantly decreased by 38.19% (p=0.004), while 37.1% of the patients experienced at least 50% decrease in the frequency of hot flashes. The mean daily score of hot flashes decreased by 44.39% (p=0.008). Also, 48.6% of the patients experienced at least a 50% reduction in the mean daily score of hot flashes.

After four weeks of megestrol use, the mean daily number of hot flashes significantly decreased by 68.93% (p<0.001). Also, 73.5% of patients experienced at least 50% decrease in the frequency of hot flashes. At the end of the study, the mean daily score of hot flashes decreased by 67.47% (p=0.001) while 70.6% of patients experienced at least 50% decrease in the mean daily score of hot flashes. Figure 3 and Figure 4 show changes in the frequency and score of hot flashes in the two groups during four weeks of intervention, respectively.

The two groups significantly differed regarding the decreased frequency of hot flashes. In other words, the mean reduction in the megestrol group after four weeks of intervention was greater than the chicory-fumitory syrup (p=0.001). Also, the percentage of patients with more than 50% reduction in the frequency of hot flashes in the

megestrol group was significantly higher than the chicory-fumitory syrup group (p=0.004).
The reduction in the daily score of hot flashes in the megestrol group was greater than in the chicory-fumitory syrup group (p=0.021). Also, changes in the daily hot flash score between the two groups were significant in the third and fourth weeks (p=0.000) and the fourth and fifth weeks (p=0.046). The response to megestrol was greater than the chicory-fumitory syrup. The two groups showed no significant difference regarding the number of patients with more than 50% reduction in the daily hot flash score (p=0.087).

Figure 5 compares megestrol and chicory-fumitory syrup groups regarding the hot flash score and the number of hot flashes.
Table 3 presents the classified response rates of subjects in the two groups regarding the number and score of hot flashes.
Seven adverse events were recorded in this trial, including four in the chicory-fumitory syrup group and three in the megestrol group (
Table **4**). All of these adverse events were mild to moderate and temporary.
At the end of the trial, the satisfaction score with the intervention was 3.91 out of 5 in the chicory-fumitory group and 4.69 in the megestrol group (p=0.059).

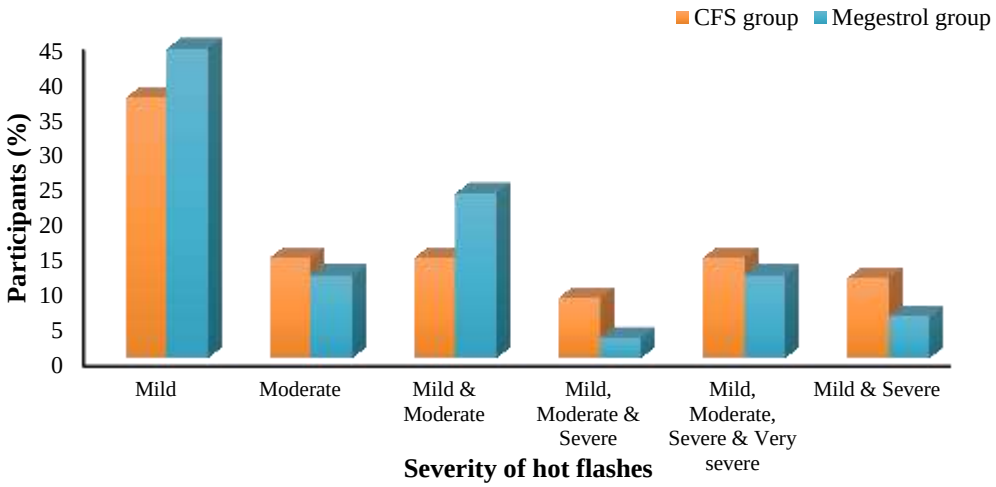

Figure 2. Severity of hot flashes in the baseline week. CFS: chicory-fumitory syrup

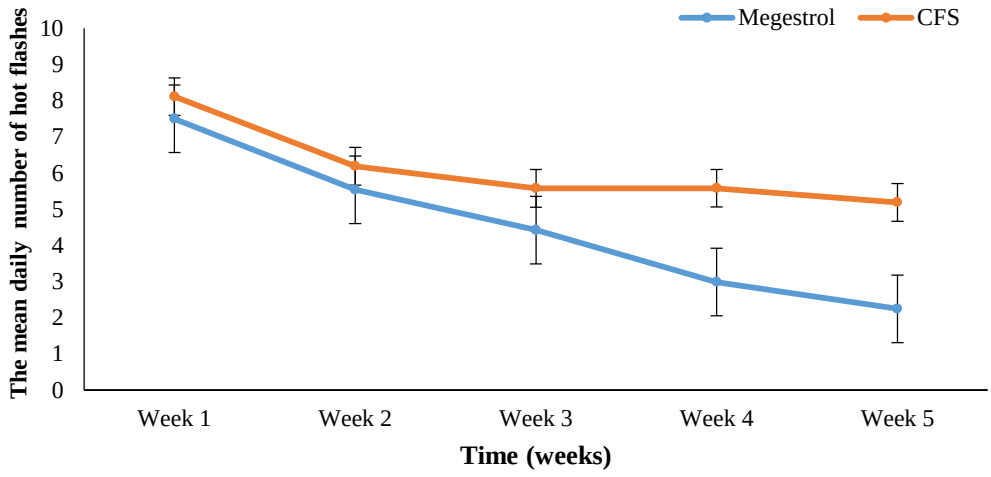

Figure 3. Changes in the mean daily number of hot flashes in the two groups during five weeks; CFS: chicory-fumitory syrup

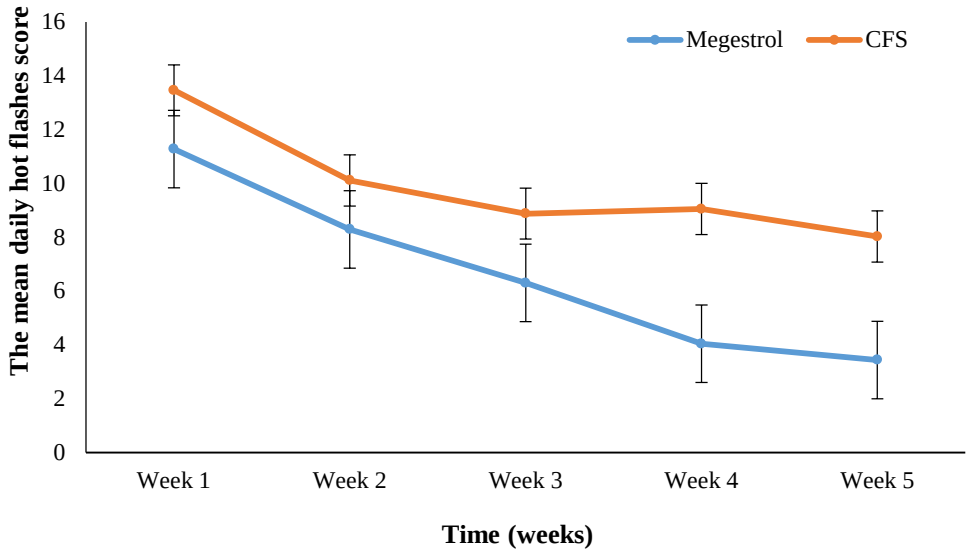

Figure 4. Changes in the mean daily hot flash score in the two groups during five weeks. CFS: chicory-fumitory syrup

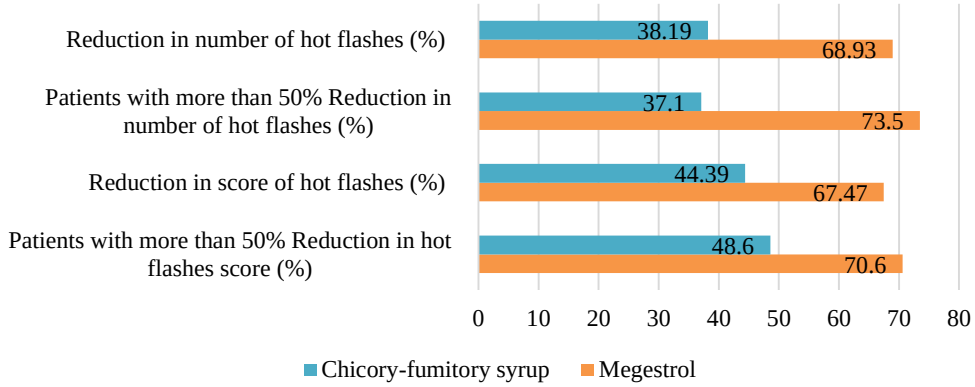

Figure 5. Comparison of changes in hot flashes in the two groups

Table 3. The patients' response in the two groups

		Percentage of hot flashes changes		Percentage of the score of hot flash changes	
Treatment group	**Response**	**Frequency**	**Percent**	**Frequency**	**Percent**
Chicory-fumitory Syrup	**<= 25%**	18	51.4	14	40.0
	25-49	4	11.4	4	11.4
	50-74	4	11.4	8	22.9
	75-100	9	25.7	9	25.7
	Total	35	100.0	35	100.0
Megestrol	**<= 25%**	5	14.7	4	11.8
	25-49	4	11.8	6	17.6
	50-74	7	20.6	5	14.7
	75-100	18	52.9	19	55.9
	Total	34	100.0	34	100.0

Table 4. Adverse events during the trial

Groups	Adverse events	Number of subjects
Chicory-fumitory Syrup	• Headache and intensified hot flashes after the first dose	1
	• Increase in hot flashes intensity	1
	• Itching of upper limbs after two weeks	1
	• Intensify of constipation after one week	1
Megestrol	• Increase of hot flashes intensity in 3 days	1
	• Chill and sensation of cold after 2 weeks	1
	• Pain and swelling of the face and hands after 3 days	1

The propensity to use traditional and complementary medicine (TCM) to manage cancer therapy-related complications is growing, especially in the last decades. Many studies on hot flashes in prostate cancer patients have focused on TCM approaches, such as acupuncture, cognitive behavioral therapy, and using herbal medicine [1,39]. Limited studies have been published on the efficacy of herbal medicine in hot flashes of prostate cancer patients undergoing ADT. A large sample size and a control group are among the advantages of the present study compared to previous studies. A recently prospective observational pilot study with 25 subjects in one herbal medicine group was published by Turco et al. (2020). The results of study indicated the efficacy of this Japanese traditional medicine in reduction of frequency and improvement of hot flashes strength [40].

In a similar study, Keishibukuryogan, a traditional Japanese Kampo medicine, showed efficacy in alleviating hot flashes in prostate cancer patients. Similar to our investigation, the hot flash intensity was improved four weeks after the intervention, but the frequency and duration of hot flashes were reduced after 8 weeks [40]. The efficacy of chicory-fumitory syrup was similar to the results reported by Vandecasteele et al. In their study, *Salvia officinalis* (sage) decreased the frequency of hot flashes to 48% and reduced the intensity of hot flashes to 43% [41]. Contrary to the results of our study, a clinical study conducted by Vitolins et al. (2013) about the efficacy of soy protein in men with hot flashes did not lead to positive results. After 12 weeks of interventions, soy protein only improved patients' quality of life [42].

Khosropanah et al. conducted a double-blinded controlled clinical trial on the efficacy of chicory-fumitory syrup (from hydroalcoholic extract of chicory seeds and aerial parts of fumitory) in hot flashes of breast cancer survivors. The results of the study were significantly higher than placebo. Also, the syrup could decrease the frequency and severity of hot flashes by 57% [27], which was higher than our study. Malekzadeh Moghani et al. (2022) have shown the efficacy of distillate of chicory and fumitory in hot flashes of women with breast cancer. The study results indicated a reduction in frequency (by 30.7%) and hot flashes score (by 41.34%) [26].

The results of our study on the effectiveness of chicory and fumitory are in line with the medical applications of these two herbs in diseases with warm temperament which were mentioned in Persian medicine resources, as well as their traditional uses.

On the other hand, despite the conventional use of megestrol for hot flashes in prostate cancer patients [43], there have been only one clinical trial [15] and two observational studies [13,38] on the efficacy and safety of megestrol for hot flashes in men under ADT. Therefore, evaluating the megestrol effects is an important issue addressed in the present study.

In this clinical trial, both megestrol and chicory-fumitory syrup could alleviate hot flashes in prostate cancer patients; nonetheless, megestrol was more potent. The low efficacy of chicory and fumitory may be due to the lower dose than the dose mentioned in Iranian traditional medicine resources. Therefore, it is recommended to examine higher doses of chicory-fumitory syrup in future studies. Traditional medicine's usual forms of chicory and fumitory are mostly decoction, mustard, or distillate. One of the advantages of this study was using a formulation based on a hydroalcoholic extract of chicory and fumitory, which is easier to consume by patients compared to traditional forms.

The efficacy of megestrol was lower than that reported in a similar study by Loprinzi et al., which showed that the same dose of megestrol could decrease the number of hot flashes by 81% and reduce the intensity of hot flashes by 84% after four weeks of intervention [15]. Similarly, in a prospective study by Smith et al., 70% of patients who received megestrol showed a complete response (no hot flashes) [13].

However, the efficacy of megestrol in managing hot flashes in breast cancer survivors varied in other clinical trials, ranging from 48% to 88% [15,44,45]. It seems that the therapeutic response of megestrol for hot flashes is different in different groups of patients.

According to the present study and similar studies, short-term use of low dose megestrol is recommended as an efficient and safe pharmacological agent for hot flashes in men with prostate cancer [15,38]. In a study by Irani et al. [46], cyproterone and medroxyprogesterone acetate were more potent than megestrol, while other drugs, such as paroxetine [47,48], gabapentin [49], clonidine [50], and venlafaxine [42,51] were less effective than megestrol in other clinical trials.

Sloan et al., in a methodological analysis of previous studies on hot flashes in cancer patients, concluded that if an intervention has more than 50% efficacy in decreasing hot flashes, it is considered effective. Although agents with an efficacy of more than 40% and less than 50% may be more effective than the placebo, the difference is marginal at best [34]. Based on the present findings, chicory-fumitory syrup was more effective than placebo, megestrol was tolerable, and only some minor side effects were reported. In our study, some of the subjects reported the exacerbation of hot flashes and the sensation of chills, which is consistent with previous studies [15,38]. The reported swelling and pain due to megestrol use may be related to the glucocorticoid-like activity of this drug [52]. Consumption of chicory-fumitory syrup was safe in most prostate cancer patients, and only four non-serious adverse effects were reported. Itching related to the use of chicory-fumitory syrup is possibly related to the hypersensitivity of some people to the herbs of the Asteraceae family such as chicory [21]. Headache was also reported as a side effect of chicory in one participant in Osler et al.'s study [53].

A limitation of this study was its non-blind design due to the unavailability of the syrup form of megestrol in the Iranian pharmaceutical market. Also, we did not have a placebo for the interventions. The placebo efficacy in previous studies on hot flashes in prostate cancer patients ranged between 20% and 30% [49,51], and the placebo effect was reported to be 21% in a study by Loprizi et al. on megestrol [15]. The effect of placebo syrup versus chicory-fumitory syrup in another study conducted on breast cancer subjects was 10% [27]; however, the present study's exact effect of chicory-fumitory syrup versus placebo remained unclear, and further placebo-controlled clinical trials are required.

Conclusion

The present study indicated that a low dose of megestrol acetate for four weeks is an effective and tolerable treatment for ADT-related hot flashes in men with prostate cancer. Chicory-fumitory syrup could be effective against hot flashes in prostate cancer patients; however, further clinical trials with larger high-quality sample sizes and a long-term follow-up are required to confirm the efficacy and safety of this herbal product.

Acknowledgments

This paper was based on the Ph.D. thesis of Dr. S. Sadeghi (NO: 206), Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Author contributions

Sajjad Sadeghi conduct clinical trial and contributed to collecting the data, investigation, data curation and writing original draft; Farzaneh Ghaffari was involved in conceptualization, editing original draft; Bahram Mofid contributed to conceptualization, methodology, resources, and supervision; Mojgan Mehri Ardestani was involved in supervision, methodology, material preparation, editing original draft; Ghazaleh Heydarirad contributed to conceptualization, data curation, validation, editing original draft, supervision and project administration.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

References

[1] Qan'ir Y, DeDeaux D, Godley PA, Mayer DK, Song L. Management of androgen deprivation therapy-associated hot flashes in men with prostate cancer. *Oncol Nurs Forum*. 2019; 46(1): 107–118.

[2] Frisk J. Managing hot flushes in men after prostate cancer, a systematic review. *Maturitas*. 2010; 65(1): 15–22.

[3] Cheung AS, de Rooy C, Hoermann R, Lim Joon D, Zajac JD, Grossmann M. Quality of life decrements in men with prostate cancer undergoing androgen deprivation therapy. *Clin Endocrinol (Oxf).* 2017; 86(3): 388–394.
[4] Gonzalez BD, Small BJ, Cases MG, Williams NL, Fishman MN, Jacobsen PB, Jim HS. Sleep disturbance in men receiving androgen deprivation therapy for prostate cancer: the role of hot flashes and nocturia. *Cancer*. 2018; 124(3): 499–506.
[5] Engstrom CA. Hot flashes in prostate cancer: state of the science. *Am J Mens Health*. 2008; 2(2): 122–132.
[6] Ulloa EW, Salup R, Patterson SG, Jacobsen PB. Relationship between hot flashes and distress in men receiving androgen deprivation therapy for prostate cancer. *Psychooncology*. 2009; 18(6): 598–605.
[7] Kumar RJ, Barqawi A, Crawford ED. Adverse events associated with hormonal therapy for prostate cancer. *Rev Urol*. 2005; Suppl 5(S5): 37–43.
[8] Higano C. Androgen deprivation therapy: monitoring and managing the complications. *Hematol Oncol Clin North Am*. 2006; 20(4): 909–923.
[9] Karling P, Hammar M, Varenhorst E. Prevalence and duration of hot flushes after surgical or medical castration in men with prostatic carcinoma. *J Urol*. 1994; 152(4): 1170–1173.
[10] Grunfeld EA, Hunter M, Yousaf O. Men's experience of a guided self-help intervention for hot flushes associated with prostate cancer treatment. *Psychol Health Med*. 2017; 22(4): 425–433.
[11] Fisher WI, Johnson AK, Elkins GR, Otte JL, Burns DS, Yu M, Carpenter JS. Risk factors, pathophysiology, and treatment of hot flashes in cancer. *CA Cancer J Clin*. 2013; 63(3): 167–192.
[12] Jones JM, Kohli M, Loprinzi CL. Androgen deprivation therapy-associated vasomotor symptoms. *Asian J Androl*. 2012; 14(2): 193–197.
[13] Smith JA. A prospective comparison of treatments for symptomatic hot flushes following endocrine therapy for carcinoma of the prostate. *J Urol*. 1994; 152(1): 132–134.
[14] Zimmerman Y, Frydenberg M, van Poppel H, van Moorselaar RJA, Roos EP, Somford DM, Roeleveld TA, de Haan TD, van Melick HH, Reisman Y. Estetrol prevents hot flushes and improves quality of life in patients with advanced prostate cancer treated with androgen deprivation therapy: the PCombi study. *Eur Urol Open Sci*. 2022; 45: 59–67.
[15] Loprinzi CL, Michalak JC, Quella SK, O'Fallon JR, Hatfield AK, Nelimark RA, Dose AM, Fischer T, Johnson C, Klatt NE. Megestrol acetate for the prevention of hot flashes. *N Engl J Med*. 1994; 331(6): 347–352.
[16] Kokorovic A, So AI, Serag H, French C, Hamilton RJ, Izard JP, Nayak JG, Pouliot F, Saad F, Shayegan B. UPDATE–Canadian urological association guideline on androgen deprivation therapy: adverse events and management strategies. *Can Urol Assoc J*. 2022; 16(8): 416–431.
[17] Johnson A, Roberts L, Elkins G. Complementary and alternative medicine for menopause. *J Evid Based Integr Med*. 2019; 24: 1–14.
[18] Guo PP, Li P, Zhang XH, Liu N, Wang J, Chen DD, Sun WJ, Zhang W. Complementary and alternative medicine for natural and treatment-induced vasomotor symptoms: an overview of systematic reviews and meta-analyses. *Complement Ther Clin Pract*. 2019; 36: 181–194.
[19] Bahmani M, Shahinfard N, Rafieian-Kopaei M, Saki K, Shahsavari S, Taherikalani M, Ghafourian S, Baharvand-Ahmadi B. Chicory: a review on ethnobotanical effects of *Cichorium intybus* L. *J Chem Pharm Sci*. 2015; 8(4): 672–682.
[20] Kumar S, Kamboj A, Sharma A. *Fumaria parviflora* Lam. (fumitory): a traditional herbal medicine with modern evidence. *Asian J Pharm Pharmacol*. 2017; 3(6): 200–207.
[21] Street RA, Sidana J, Prinsloo G. *Cichorium intybus*: traditional uses, phytochemistry, pharmacology, and toxicology. *Evid Based Complement Alternat Med*. 2013; Article ID 579319.
[22] Perović J, Šaponjac VT, Kojić J, Krulj J, Moreno DA, García-Viguera C, Bodroža-Solarov M, Ilić N. Chicory (*Cichorium intybus* L.) as a food ingredient–nutritional composition, bioactivity, safety, and health claims: a review. *Food Chem*. 2021; Article ID 127676.
[23] Shirzad M, Rahimi R, Soleymani S, Hosein Salari A, Ghadami S, Khalaj A, Hamzeloo-

Moghadam M, Taleb A, Hajimehdipoor H, Amin G. Chicory ("Kasni"). *J Islamic Iran Trad Med*. 2020; 11(3): 295–306.
[24] Aghili MH. Makhzan-al-advie. Tehran: Tehran University of Medical Sciences, 2009.
[25] Ashayeri N, Abbasian A, Janbakhsh S, Shibani S, Sodagari F, Minai B. The more prevalent medicinal herbs which have been purchased from herbal medicine stores in Tehran, 2008. *J Islamic Iran Trad Med.* 2013; 3(4): 477–482.
[26] Moghani MM, Moghtadaei S, Sonboli A, Sadeghi S, Riahi SM, Heydarirad G. Effects of chicory and fumitory on hot flashes of breast cancer survivors compared to venlafaxine: a randomized clinical trial. *J Complement Med Res*. 2022; 12(4): 200–210.
[27] Khosropanah A, Mehri Ardestani M, Rostami N, Hashemi F, Pasalar M, Hunter J, Heydarirad G. Effects of chicory and fumitory on hot flashes among breast cancer survivors: a randomized, double-blind placebo-controlled trial. *J Integr Complement Med*. 2023; 29(1): 31–41.
[28] The United States Pharmacopeial Convention. United States Pharmacopeia National Formulary (USP 37–NF 32). Rockville: United States Pharmacopeial Convention, 2012.
[29] Slinkard K, Singleton VL. Total phenol analysis: automation and comparison with manual methods. *Am Soc Enol Viticulture.* 1977; 28: 49–55.
[30] Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, LaVasseur BI, Barton DL, Novotny PJ, Dakhil SR, Rodger K, Rummans TA. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet*. 2000; 356(9247): 2059–2063.
[31] Loprinzi CL, Barton DL, Sloan JA, Zahasky KM, De Anne RS, Pruthi S, Novotny PJ, Perez EA, Christensen BJ. Pilot evaluation of gabapentin for treating hot flashes. *Mayo Clin Proc*. 2002; 77(11): 1159–1163.
[32] Barton DL, Loprinzi CL, Quella SK, Sloan JA, Veeder MH, Egner JR, Fidler P, Stella PJ, Swan DK, Vaught NL. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol*. 1998; 16(2): 495–500.
[33] Guttuso Jr T, DiGrazio WJ, Reddy SY. Review of hot flash diaries. *Maturitas.* 2012; 71(3): 213–216.
[34] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl H. Methodologic lessons learned from hot flash studies. *J Clin Oncol*. 2001; 19(23): 4280–4290.
[35] Editorial board. PDR for herbal medicines. Montvale: Medical Economics Company Pub, 2000.
[36] Nishimura M, Ohkawara T, Kanayama T, Kitagawa K, Nishimura H, Nishihira J. Effects of the extract from roasted chicory (*Cichorium intybus* L.) root containing inulin-type fructans on blood glucose, lipid metabolism, and fecal properties. *J Tradit Complement Med*. 2015; 5(3): 161–167.
[37] Mandgary A, Enayati M. Antinociceptive effects and toxicity of *Fumaria parviflora* Lam. in mice and rats. *Daru J Pharm Sci*. 2004; 12(4): 136–140.
[38] Quella SK, Loprinzi CL, Sloan JA, Vaught NL, DeKrey WL, Fischer T, Finck G, Pierson N, Pisansky T. Long term use of megestrol acetate by cancer survivors for the treatment of hot flashes. *Cancer*. 1998; 82(9): 1784–1788.
[39] Hutton B, Hersi M, Cheng W, Pratt M, Barbeau P, Yazdi F, Mazzarello S, Ahmadzai N, Skidmore B, Morgan SC. Comparing pharmacologics, natural health products, physical and behavioral interventions for management of hot flashes in patients with breast and prostate cancer: a systematic review with meta-analyses. *Oncol Nurs Forum*. 2020; 47(4): 86–106.
[40] Shigehara K, Izumi K, Nakashima K, Kawaguchi S, Nohara T, Kadono Y, Mizokami A. Efficacy and safety of Keishibukuryogan, a traditional Japanese Kampo medicine, for hot flashes in prostate cancer patients receiving androgen deprivation therapy. *Transl Androl Urol*. 2020; 9(6): 2533–2540.
[41] Vandecasteele K, Ost P, Oosterlinck W, Fonteyne V, De Neve W, De Meerleer G. Evaluation of the efficacy and safety of *Salvia officinalis* in controlling hot flashes in prostate cancer patients treated with androgen deprivation. *Phytother Res*. 2012; 26(2): 208–213.
[42] Vitolins MZ, Griffin L, Tomlinson WV, Vuky J, Adams PT, Moose D, Frizzell B, Lesser GJ, Naughton M, Radford Jr JE.

Randomized trial to assess the impact of venlafaxine and soy protein on hot flashes and quality of life in men with prostate cancer. *J Clin Oncol*. 2013; 31(32): 4092–4098.

[43] Turco F, Di Prima L, Pisano C, Poletto S, De Filippis M, Crespi V, Farinea G, Cani M, Calabrese M, Saporita I. How to improve the quality of life of patients with prostate cancer treated with hormone therapy? *Res Rep Urol*. 2023; 15: 9–26.

[44] Goodwin JW, Green SJ, Moinpour CM, Bearden III JD, Giguere JK, Jiang CS, Lippman SM, Martino S, Albain KS. Phase III randomized placebo-controlled trial of two doses of megestrol acetate as treatment for menopausal symptoms in women with breast cancer: Southwest Oncology Group Study 9626. *J Clin Oncol*. 2008; 26(10): 1650–1656.

[45] Bertelli G, Venturini M, Del Mastro L, Bergaglio M, Sismondi P, Biglia N, Venturini S, Porcile G, Pronzato P, Costantini M. Intramuscular depot medroxyprogesterone versus oral megestrol for the control of postmenopausal hot flashes in breast cancer patients: a randomized study. *Ann Oncol*. 2002; 13(6): 883–888.

[46] Irani J, Salomon L, Oba R, Bouchard P, Mottet N. Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomised trial. *Lancet Oncol*. 2010; 11(2): 147–154.

[47] Loprinzi CL, Barton DL, Carpenter LA, Sloan JA, Novotny PJ, Gettman MT, Christensen BJ. Pilot evaluation of paroxetine for treating hot flashes in men. *Mayo Clin Proc*. 2004; 79(10): 1247–1251.

[48] Naoe M, Ogawa Y, Shichijo T, Fuji K, Fukagai T, Yoshida H. Pilot evaluation of selective serotonin reuptake inhibitor antidepressants in hot flash patients under androgen-deprivation therapy for prostate cancer. *Prostate Cancer Prostatic Dis*. 2006; 9(3): 275–278.

[49] Loprinzi CL, Dueck A, Khoyratty B, Barton D, Jafar S, Rowland Jr K, Atherton P, Marsa G, Knutson W, Bearden III JD. A phase III randomized, double-blind, placebo-controlled trial of gabapentin in the management of hot flashes in men (N00CB). *Ann Oncol*. 2009; 20(3): 542–549.

[50] Loprinzi CL, Goldberg RM, O'Fallon JR, Quella SK, Miser AW, Mynderse LA, Brown LD, Tschetter LK, Wilwerding MB, Dose AM. Transdermal clonidine for ameliorating post-orchiectomy hot flashes. *J Urol*. 1994; 151(3): 634–636.

[51] Quella SK, Loprinzi CL, Sloan J, Novotny P, Perez EA, Burch PA, Antolak Jr SJ, Pisansky TM. Pilot evaluation of venlafaxine for the treatment of hot flashes in men undergoing androgen ablation therapy for prostate cancer. *J Urol*. 1999; 162(1): 98–102.

[52] Yeh SS, Schuster MW. Megestrol acetate in cachexia and anorexia. *Int J Nanomed*. 2006; 1(4): 411–416.

[53] Olsen NJ, Branch VK, Jonnala G, Seskar M, Cooper M. Phase 1, placebo-controlled, dose escalation trial of chicory root extract in patients with osteoarthritis of the hip or knee. *BMC Musculoskelet Disord*. 2010; 11: 1–7.

Abbreviations

SSRIs: selective serotonin reuptake inhibitors; CSF: chicory-fumitory syrup