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Comparison of Chicory–Fumitory Syrup and Megestrol for the Management of Hot Flashes in Prostate Cancer Patients Undergoing Androgen Deprivation Therapy

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ABSTRACT

Hot flashes rank as one of the most frequent and disruptive adverse reactions to androgen deprivation therapy (ADT) among men treated for prostate cancer. In the absence of an established standard therapy, more studies are needed to establish safe and effective management options. This randomized controlled trial involved prostate cancer patients on ADT who were randomly assigned to receive either chicory-fumitory syrup (derived from hydroalcoholic extracts of chicory and fumitory) or megestrol. Subjects logged the daily frequency and intensity of hot flashes for one week before starting treatment (baseline). They then took the assigned intervention—syrup (5 mL twice daily) or megestrol (20 mg twice daily)—for four weeks while maintaining the diary. The study was completed by 69 participants (35 in the chicory-fumitory arm and 34 in the megestrol arm). After four weeks, the chicory-fumitory group experienced a 38.19% reduction in mean daily hot flash frequency ($p=0.004$) and a 44.39% drop in hot flash score ($p=0.008$). The megestrol group showed a 68.93% decline in frequency ($p<0.001$) and a 67.47 reduction in score ($p=0.001$). Independent samples t-test revealed significantly greater improvements in both frequency and severity in the megestrol arm compared to the chicory-fumitory arm ($p=0.001$ and $p=0.021$, respectively). Chicory-fumitory syrup provides meaningful relief from hot flashes in prostate cancer patients on ADT, though megestrol achieved markedly superior reductions in both frequency and intensity. Larger trials with extended treatment duration are warranted to further evaluate the potential of chicory and fumitory in this setting.

Keywords: Chicory, Fumitory, Hot flashes, Megestrol, Prostate cancer, Iranian traditional medicine

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Introduction

Hot flashes constitute a widespread and often debilitating complication of androgen deprivation therapy (ADT), the cornerstone treatment for advanced prostate cancer [1, 2]. They substantially impair quality of life [3], disrupt sleep patterns [4], alter mood and interpersonal interactions [5], and generate considerable emotional burden [6]; in some instances, the severity leads patients to abandon therapy altogether [2]. Clinically, hot flashes present as abrupt episodes of intense warmth accompanied by sweating and skin flushing, lasting anywhere from seconds to an hour [7]. Recurrence is common, and episodes may include nausea, restlessness, or heightened anxiety [8]. Importantly, these symptoms frequently endure long-term, retaining comparable intensity and duration even after ADT discontinuation [2, 9]. The primary pathophysiological explanation centers on hypothalamic thermoregulatory instability triggered by fluctuations in sex steroids, which in turn affect central neurotransmitters and compromise temperature control [10].

In recent decades, multiple trials have assessed pharmacological strategies for managing hot flashes in this population. Hormonal agents evaluated include diethylstilbestrol, cyproterone acetate, medroxyprogesterone acetate, megestrol acetate, estetrol, alongside non-hormonal options such as phenobarbital-ergotamine combinations, gabapentin, clonidine, venlafaxine, and paroxetine. Outcomes have been mixed, with many

regimens associated with undesirable effects like weight increase, tiredness, breathlessness, gynecomastia, and PSA elevations [1, 11-14]. Certain investigations have highlighted megestrol as helpful for symptom control in prostate cancer survivors [13, 15]. Despite this, no universally accepted pharmacological standard exists, largely due to limited data on long-term efficacy and tolerability [16].

Interest has also grown in traditional and complementary approaches. Research has examined modalities including acupuncture, cognitive behavioral interventions, and various botanicals such as soy, flaxseed, and sage [1, 17, 18]. Cichorium intybus L. (commonly known as chicory) and Fumaria parviflora Lam. (fumitory) represent two medicinal plants with a longstanding history in ancient Persian therapeutic practices [19, 20]. Scientific investigations have established their diverse pharmacological actions, encompassing antioxidant, anti-inflammatory, pain-relieving, antiallergic, liver-protective, stomach-protective, itch-relieving, insect-repellent, antiprotozoal, blood-sugar-lowering, antibacterial, antinociceptive, and anticancer effects [20, 21]. Beyond basic nutritional elements like fats, proteins, minerals, and vitamins, chicory is particularly abundant in active phytochemicals, including inulin, sesquiterpene lactones, flavonoids, alkaloids, steroids, terpenoids, β-carotene, zeaxanthin, hydroxycoumarins, caffeic acid derivatives, and essential oils [22]. Fumitory contains notable compounds such as fumarine, protopine, caffeic acid, parfumine, oxyberberine, protocatechuic acid, cryptopine, berberine, and sesquiterpenoids [20].

According to traditional Persian medical theory, chicory possesses a cold and moist nature, providing advantages like easing thirst, balancing excess yellow bile (Safra), soothing gastric irritation, unblocking liver pathways, moderating liver warmth, and cleansing the blood. It further aids the urinary tract and kidneys while addressing specific headache varieties [23, 24]. Fumitory, characterized by a temperate-dry quality, proves valuable for ailments involving the stomach, liver, spleen, oral cavity, and skin [24].

Ancient Persian scholarly works advocate the use of chicory and fumitory for conditions marked by excessive warmth and sudden reddening, including fevers, heightened body heat, and vasomotor flushes [24]. These plants have also been employed in folk traditions to counteract hot flashes [25]. Modern randomized trials have validated their role in diminishing hot flash symptoms in women who have overcome breast cancer [26, 27]. To date, however, their potential benefits for hot flashes in male prostate cancer patients remain unexplored. Accordingly, this randomized controlled study sought to compare the impact of a Persian herbal syrup formulated from chicory and fumitory against megestrol—a widely recognized pharmaceutical option—on hot flash management in men receiving androgen deprivation therapy for prostate cancer.

Materials and Methods

Plant material

Dried above-ground portions of chicory (Cichorium intybus L.) and fumitory (Fumaria parviflora Lam.) were acquired from a trusted herbal vendor in Tehran during 2017. Botanical verification was conducted by an expert at the Herbarium of the Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. Reference samples were archived at the same institution's herbarium, assigned voucher numbers MPH-2762 (chicory) and MPH-2763 (fumitory).

Preparation

The study intervention was a syrup made from combined hydroalcoholic extracts of chicory and fumitory. Production began with thorough cleansing of the raw herbs to eliminate dirt and debris, followed by drying and pulverization. Extraction involved maceration in 70% ethanol. The liquid extract was then evaporated under reduced pressure in a rotary evaporator and solidified via lyophilization. Next, 36 grams of lyophilized chicory extract and 18 grams of lyophilized fumitory extract were incorporated into 120 mL of a 70% (w/w) aqueous sucrose solution and homogenized. This formulation ensured that every 5 mL serving provided 1.5 g of chicory dried extract and 0.75 g of fumitory dried extract.

The finished syrup was dispensed into 240 mL amber plastic containers, properly labeled, and kept in a cool, dry, light-protected area.

Safety assessments included microbial and fungal contamination checks through measurement of total aerobic microbial count (TAMC) and total yeast/mold count (TYMC), plus targeted screening for Escherichia coli and Salmonella species, meeting the quality standards specified by the United States Pharmacopeia [28].

Total phenolics content

To ensure standardization of the herbal product, the total phenolic content was quantified as a quality marker via spectrophotometry, employing the standard Folin–Ciocalteu assay protocol [29].

Study design

This randomized controlled trial took place at the oncology clinic of Shahid Labbafinejad Medical Center in Tehran, Iran, from January 2018 to September 2019. The design followed the approach originally described by Loprinzi CL *et al*. in 1994 [15], a methodology widely adopted in subsequent research assessing hot flashes among individuals with prostate or breast cancer [30-32]. The trial spanned five weeks: one week for baseline assessment followed by four weeks of treatment. During the baseline period, participants solely documented the daily frequency and intensity of hot flashes in a provided diary [33]. Following this, patients initiated their assigned treatments while continuing to log hot flash occurrences over the next four weeks.

The trial featured two parallel groups: one receiving chicory-fumitory syrup and the other megestrol. After completion of the baseline week, eligible participants were assigned to groups using simple randomization generated by software (Random Rx Ver.1). Those in the intervention arm took 5 mL of chicory-fumitory syrup twice daily, whereas the control arm received 20 mg of megestrol twice daily, for a duration of four weeks.

Study population

Men with prostate cancer experiencing hot flashes while on androgen deprivation therapy (ADT) were identified and referred by a uro-oncologist. The investigator then screened candidates for eligibility, and those who met criteria and agreed to join were required to provide signed informed consent.

Inclusion criteria

(1) Receiving ADT for longer than eight weeks prior to enrollment; (2) reporting hot flashes for at least four weeks before entering the study; (3) experiencing a minimum of two hot flash episodes per day.

Exclusion criteria

Individuals currently receiving chemotherapy or radiotherapy, those who had used antidepressants (such as SSRIs) within the preceding four weeks, and patients with severe renal, hepatic, coagulopathy, or vascular conditions were not included.

Participants were informed of their right to discontinue participation at any point without penalty. They were also instructed to promptly report any emerging symptoms or significant adverse effects throughout the trial.

Outcome measures

The primary endpoints were the average daily frequency of hot flashes and the average daily hot flash severity score. Frequency was derived directly from diary entries. The severity score was computed using the formula:

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

Patients classified hot flash severity themselves according to guidelines in their diary [33]. This four-level classification system, originally created by Sloan *et al*. [34], has been validated and applied in later investigations. Detailed written instructions distinguishing severity levels, along with daily diary templates, were supplied to all participants.

For both endpoints, the mean value from the final week of treatment was compared against the baseline week for each individual. At study conclusion, participants rated their overall satisfaction with the assigned treatment on a 5-point Likert scale, where one indicated "not satisfied" and five indicated "very satisfied."

Safety assessment

Dosing for the chicory-fumitory syrup was established based on contemporary studies and established traditional recommendations for these herbs [35-37]. Megestrol dosing aligned with protocols from comparable trials [13, 15, 38]. Throughout the study period, all enrolled individuals were monitored for potential adverse reactions or toxic effects and encouraged to contact the investigator if concerns arose.

Sample size

In line with findings from a prior investigation [15], the calculation incorporated an anticipated 50% reduction in hot flash frequency, an alpha of 5%, a power (1–β) of 0.80, a standard deviation (SD) of 6.3, and a 10% dropout rate across the study duration. Accordingly, the methodologist established a target of 35 individuals per arm. This sizing allowed for detection of a 4.5-unit difference in mean daily hot flashes, aligned with a 50% drop in the overall hot flash score.

Statistical analysis

Pre- and post-intervention quantitative data were evaluated through Wilcoxon signed-rank tests or paired t-tests as appropriate. Categorical variables were contrasted using the Chi-square test. Inter-group comparisons over multiple time points employed repeated measures ANOVA. The Shapiro-Wilk test verified assumptions of normality, with statistical significance defined at 0.05. Forms were reviewed for data entry, and all analyses were conducted via SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results and Discussion

Total phenolic content in the syrup measured 5.18±0.148 mg gallic acid equivalent (GAE) per mL. All assayed parameters remained within acceptable limits.

Across the trial, 201 oncologist-referred patients underwent initial screening. Eligibility was confirmed for 117 men, who were then randomized to either megestrol (n=61) or chicory-fumitory syrup (n=56). Analysis ultimately included 69 completers (34 in megestrol and 35 in chicory-fumitory syrup) **(Figure 1).**

Participants had an overall mean age of 67.4 years (67.11 years for chicory-fumitory syrup recipients and 66.97 years for megestrol recipients). Predominantly retired and holding education below diploma level, their demographics appear in **Table 1**. No meaningful inter-group differences emerged on Chi-square or Fisher's exact testing ($p>0.05$). Roughly half reported hot flashes persisting beyond nine months. Pre-study ADT exposure averaged 14.21 months in the chicory-fumitory syrup arm and 13.52 months in the megestrol arm. During the baseline week, median daily hot flash counts stood at 8.10 for chicory-fumitory syrup and 7.49 for megestrol, while mean daily hot flash scores registered 13.46 and 11.28, respectively. Groups exhibited comparability in baseline hot flash frequency, scoring, and associated parameters ($p>0.05$) **(Table 2).**

During the baseline period, mild-to-moderate hot flash intensity predominated in both arms (65.7% among chicory-fumitory syrup users and 79.4% among megestrol users) **(Figure 2).**

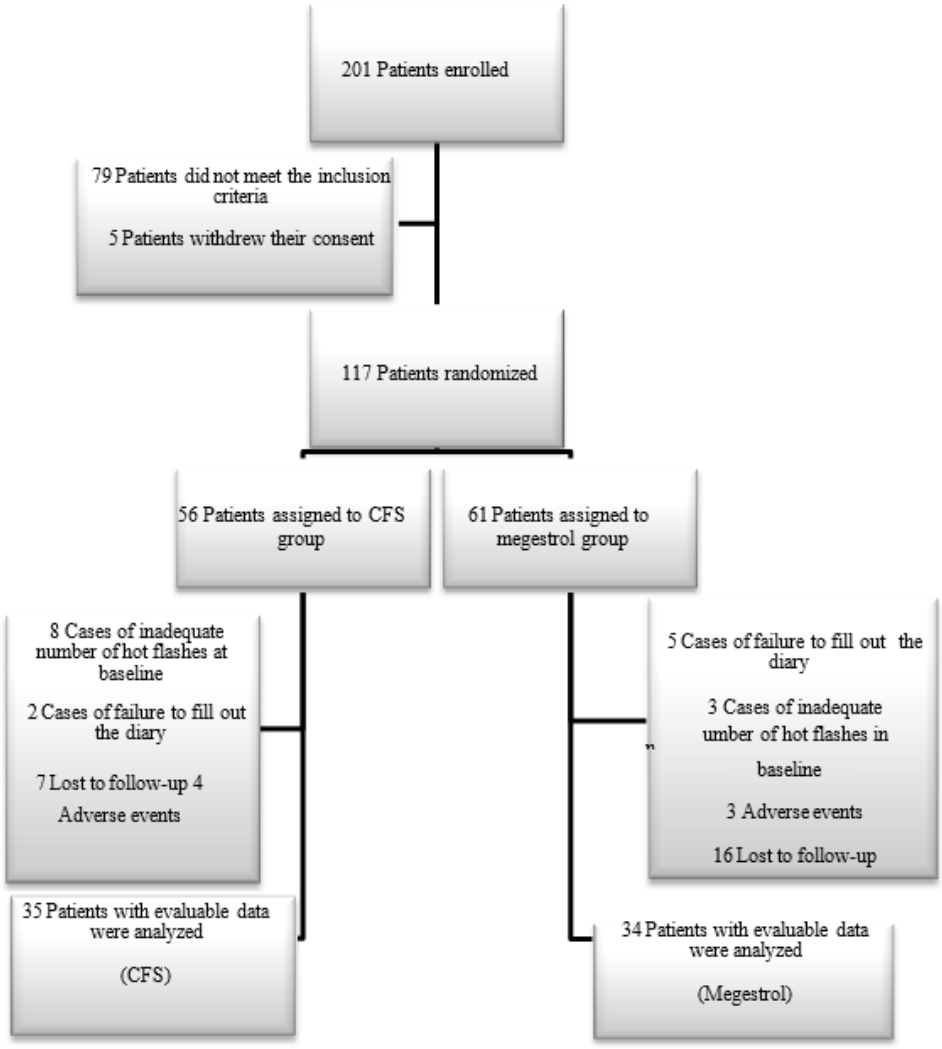

Figure 1. Consort flow chart of the trial; CFS: chicory-fumitory syrup.

Table 1. Characteristics of the participants

Variable	Chicory–Fumitory Syrup		Megestrol		p-value
	No. / Mean (SD)	%	No. / Mean (SD)	%	
Age (years)	67.11 (8.415)	—	66.97 (8.701)	—	0.945
Body mass index (kg/m²)	27.32 (4.19404)	—	26.49 (3.67795)	—	0.403
Educational level					0.978
Primary education	8	25	9	29	
Below diploma	20	62.5	15	48.4	
University graduate	4	12.5	7	22.6	
Employment status					0.934
Employed	10	30.3	10	31.3	
Retired	23	69.7	22	68.7	
Type of androgen deprivation therapy (ADT)					1.000
Pharmacological hormone therapy	32	95	31	94	
Surgical castration (orchiectomy)	2	5	2	6	
Smoking status					1.000
Smoker	4	13.3	4	14.3	
Non-smoker	26	86.7	24	85.7	
History of substance use					0.306
Yes	2	10.5	3	30	

No	17	89.5	7	70	
History of radical prostatectomy					0.079
Yes	26	86.7	16	66.7	
No	4	13.3	8	33.3	
History of chemotherapy					0.456
Yes	3	9.1	5	17.2	
No	30	90.9	24	82.8	
History of radiotherapy					0.957
Yes	18	56.3	15	55.6	
No	14	43.7	12	44.4	

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

Variable	**Chicory–Fumitory Syrup**		**Megestrol**		**p-value**
	No. / Mean (SD)	%	No. / Mean (SD)	%	
Duration of hot flash symptoms					0.901
≥ 9 months	17	50	17	51.5	
< 9 months	17	50	16	48.5	
Estimated daily frequency of hot flashes prior to enrollment					0.598
1–3 episodes	9	39.1	7	36.8	
4–9 episodes	11	47.8	10	52.6	
≥ 10 episodes	3	13	2	10.5	
Mean estimated number of daily hot flashes before intervention	5.30 (4.084)	—	4.79 (2.446)	—	0.598
Mean daily hot flash frequency at baseline	8.10 (6.00)	—	7.49 (6.11)	—	0.676
Baseline daily hot flash severity score	13.46 (13.26)	—	11.28 (13.08)	—	0.494

After four weeks of treatment with chicory-fumitory syrup, the average daily frequency of hot flashes dropped significantly by 38.19% (p=0.004), with 37.1% of participants experiencing a reduction of at least 50% in hot flash episodes. The mean daily hot flash severity score fell by 44.39% (p=0.008), and 48.6% of patients achieved at least a 50% decrease in their daily score.

In the megestrol group, after four weeks, the mean daily number of hot flashes decreased markedly by 68.93% (p<0.001), and 73.5% of patients reported a reduction of 50% or more in frequency. At study completion, the average daily hot flash score had declined by 67.47% (p=0.001), with 70.6% of participants showing at least a 50% improvement in score. **Figures 3 and 4** depict the progression of hot flash frequency and severity scores, respectively, across the two groups over the four-week treatment period.

A statistically significant difference in frequency reduction was observed between the groups: the megestrol group showed a substantially larger decrease after four weeks compared to the chicory-fumitory syrup group (p=0.001). Likewise, the proportion of patients achieving a ≥50% reduction in hot flash frequency was markedly higher with megestrol (p=0.004).

The megestrol group also exhibited a greater reduction in daily hot flash score than the chicory-fumitory syrup group (p=0.021). Significant between-group differences in daily score changes were noted during weeks 3–4 (p=0.000) and weeks 4–5 (p=0.046). Overall, megestrol produced a superior response compared to chicory-fumitory syrup. However, the proportion of patients with ≥50% reduction in daily hot flash score did not differ significantly between the groups (p=0.087).

Figure 5 contrasts the changes in hot flash frequency and score between the megestrol and chicory-fumitory syrup groups.

Table 3 summarizes the categorized response levels for hot flash frequency and score in both groups.

Seven mild-to-moderate, self-limiting adverse events were reported during the trial: four in the chicory-fumitory syrup group and three in the megestrol group **(Table 4).**

At the trial's conclusion, mean patient satisfaction scores were 3.91/5 in the chicory-fumitory syrup group and 4.69/5 in the megestrol group (p=0.059).

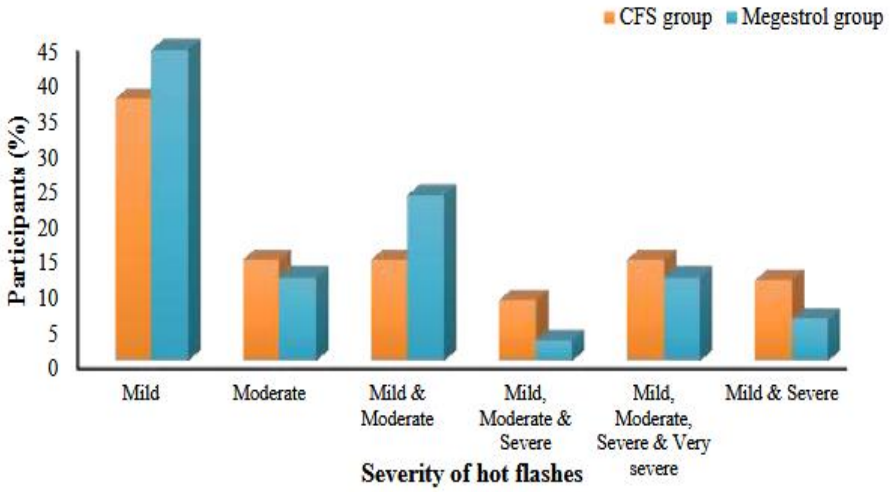

Figure 2. Baseline week hot flash severity. CFS: chicory-fumitory syrup

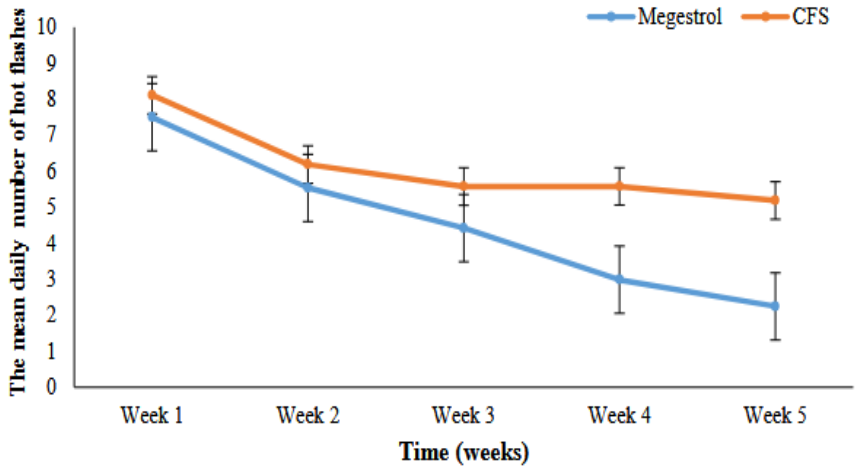

Figure 3. Weekly changes in mean daily hot flash frequency over five weeks in both groups; CFS: chicory-fumitory syrup

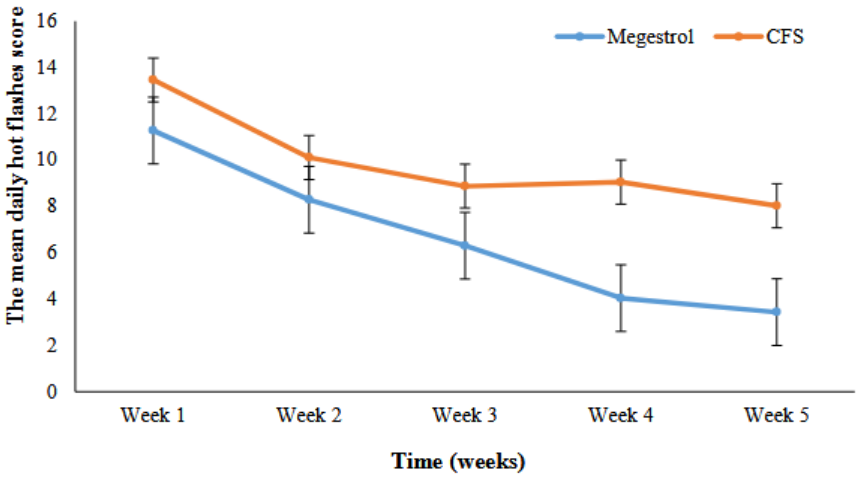

Figure 4. Weekly changes in mean daily hot flash score over five weeks in both groups. CFS: chicory-fumitory syrup

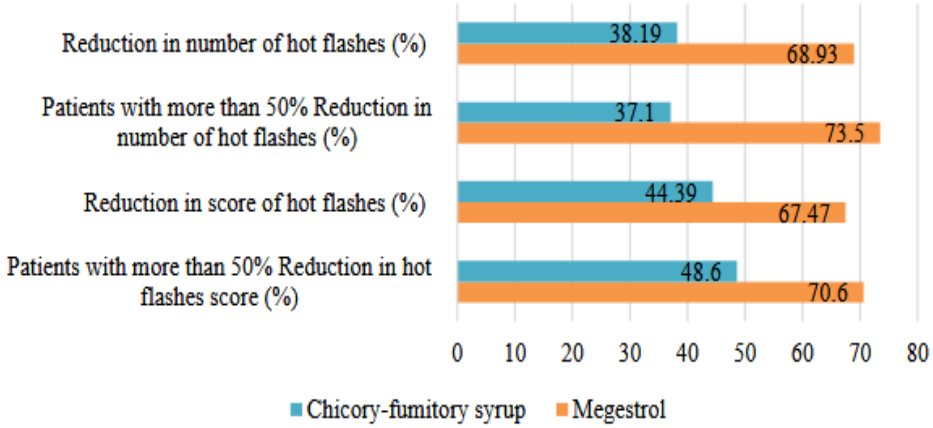

Figure 5. Comparative changes in hot flashes between the two groups

Table 3. Response categories in the two groups

Treatment Arm	Response Category (%)	Change in Hot Flash Frequency		Change in Hot Flash Severity Score	
		Frequency (n)	Percent (%)	Frequency (n)	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	—	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 observed during the trial

Treatment Group	Reported Adverse Effect	Number of Participants
Chicory–Fumitory Syrup	Headache accompanied by worsening of hot flashes following the initial dose	1
	Increased severity of hot flashes	1
	Pruritus of the upper extremities observed after two weeks	1
	Exacerbation of constipation after one week of treatment	1
Megestrol	Increased hot flash severity within three days of treatment	1
	Chills and a sensation of cold reported after two weeks	1
	Facial and hand pain with swelling occurring three days after initiation	1

The use of traditional and complementary medicine (TCM) to alleviate side effects of cancer therapy has gained considerable popularity over recent decades. Numerous investigations into hot flashes in prostate cancer patients have explored TCM options such as acupuncture, cognitive behavioral therapy, and herbal remedies [1, 39]. However, few studies have specifically assessed herbal medicine for hot flashes in men receiving androgen deprivation therapy (ADT). The present study stands out due to its larger sample size and inclusion of a control group compared to earlier research. A recent prospective pilot study by Turco *et al*. (2020) involving 25 patients treated with a single Japanese herbal formulation demonstrated reductions in hot flash frequency and improvements in severity [40].

Similarly, Keishibukuryogan, another traditional Japanese Kampo remedy, was effective in reducing hot flashes in prostate cancer patients. Consistent with our findings, it improved hot flash intensity within four weeks, though frequency and duration improvements appeared only after eight weeks [40]. The results with chicory-fumitory syrup were comparable to those reported by Vandecasteele *et al*., where Salvia officinalis (sage) reduced hot flash frequency by 48% and intensity by 43% [41]. In contrast, a clinical trial by Vitolins *et al*. (2013) found that soy protein supplementation in men with hot flashes did not significantly alleviate symptoms; after 12 weeks, only quality of life showed improvement [42].

Khosropanah *et al*. performed a double-blind, placebo-controlled clinical trial evaluating the effectiveness of chicory-fumitory syrup (prepared from hydroalcoholic extracts of chicory seeds and fumitory aerial parts) for managing hot flashes in breast cancer survivors. Their findings demonstrated significantly superior outcomes compared to placebo. Moreover, the syrup reduced both the frequency and severity of hot flashes by 57% [27], a greater improvement than observed in our investigation. Malekzadeh Moghani *et al*. (2022) demonstrated the benefits of chicory and fumitory distillate for hot flashes in breast cancer patients, reporting reductions of 30.7% in frequency and 41.34% in hot flash score [26].

The outcomes of our research regarding the benefits of chicory and fumitory align with their described applications in Persian medicine texts for conditions characterized by warm temperament, as well as their established traditional uses.

Conversely, although megestrol is commonly employed for hot flashes in prostate cancer patients [43], only one clinical trial [15] and two observational studies [13, 38] have examined its efficacy and safety in men receiving androgen deprivation therapy (ADT). Thus, assessing megestrol's impact represents a key contribution of the current study.

In this trial, both megestrol and chicory-fumitory syrup mitigated hot flashes in prostate cancer patients, although megestrol proved more effective. The relatively modest impact of chicory and fumitory might stem from using a lower dose than recommended in Iranian traditional medicine sources. Accordingly, future investigations should explore higher doses of chicory-fumitory syrup. Traditional preparations of these herbs typically involve decoctions, poultices, or distillates. A strength of this study lies in employing a hydroalcoholic extract-based formulation, which offers greater convenience for patient consumption compared to conventional forms.

Megestrol's effectiveness in our trial was lower than that documented by Loprinzi *et al*., where the identical dose achieved an 81% reduction in hot flash frequency and an 84% decrease in severity after four weeks [15]. Likewise, in a prospective investigation by Smith *et al*., 70% of megestrol-treated patients exhibited a complete response (absence of hot flashes) [13].

Nevertheless, megestrol's performance in alleviating hot flashes among breast cancer survivors has shown variability across clinical trials, with reductions ranging from 48% to 88% [15, 44, 45]. This suggests that megestrol's therapeutic response for hot flashes may vary across patient populations.

Based on our results and comparable research, short-term administration of low-dose megestrol is advisable as a safe and effective option for managing hot flashes in prostate cancer patients [15, 38]. In research by Irani *et al*. [46], cyproterone and medroxyprogesterone acetate outperformed megestrol, whereas agents like paroxetine [47, 48], gabapentin [49], clonidine [50], and venlafaxine [42, 51] demonstrated inferior efficacy in separate trials.

Sloan *et al*., through a methodological review of prior hot flash studies in cancer patients, determined that interventions achieving over 50% reduction in hot flashes qualify as effective. Treatments yielding 40–50% efficacy might surpass placebo, but the advantage is often minimal [34]. In line with these criteria, our data indicate that chicory-fumitory syrup outperformed placebo, megestrol was well-tolerated, and only mild adverse effects occurred. Certain participants noted worsened hot flashes or chills, findings echoed in earlier reports [15, 38]. Swelling and pain associated with megestrol could be linked to its glucocorticoid-like properties [52]. Chicory-fumitory syrup proved safe for most prostate cancer patients, with only four minor adverse events recorded. Itching potentially arising from the syrup may reflect hypersensitivity to Asteraceae family plants, including chicory [21]. Headache as a chicory-related side effect was also noted in one patient in Osler *et al*.'s work [53].

A key limitation of this study was its open-label design, necessitated by the lack of a syrup formulation of megestrol on the Iranian market. Additionally, no placebo was included for either treatment. Prior studies on hot flashes in prostate cancer patients reported placebo effects of 20–30% [49, 51], with Loprinzi *et al*. documenting 21% for megestrol [15]. In another trial involving breast cancer patients, placebo syrup versus chicory-fumitory

syrup yielded a 10% difference [27]; consequently, the precise superiority of chicory-fumitory syrup over placebo in our study remains uncertain, warranting additional placebo-controlled trials.

Conclusion

This study demonstrates that four weeks of low-dose megestrol acetate provides an effective and well-tolerated approach for managing ADT-induced hot flashes in prostate cancer patients. Chicory-fumitory syrup shows potential benefits against hot flashes in this population; however, larger, high-quality clinical trials with extended follow-up are needed to establish its efficacy and long-term safety.

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Conflict of Interest: None

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Ethics Statement: The protocol for this randomized controlled trial was endorsed by the institutional review board at Shahid Beheshti University of Medical Sciences in Tehran, Iran (approval code: IR.SBMU.RETECH.REC.1397.826), in full compliance with the Helsinki Declaration. Every participant gave voluntary written consent. Furthermore, the study was officially listed in the Iranian Registry of Clinical Trials (registration code: IRCT20190112042333N1).

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