TRADITIONAL AND INTEGRATIVE MEDICINE

Trad Integr Med, Volume 10, Issue 3, Summer 2025

Original Research

Formulation of *Viola odorata* L. Tablet and Evaluation of the Product Effect on Breast Cancer-Related Fatigue: A Randomized, Controlled Pilot Trial

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Received: 1 Oct 2024 **Revised:** 20 Jan 2025 **Accepted:** 18 Feb 2025

Abstract

This study was designed to formulate a *Viola odorata* L. tablet (VOT) and evaluate its efficacy in managing cancer-related fatigue (CRF) in breast cancer patients undergoing radiotherapy. The tablet was formulated and subjected to quality control tests. The pilot study was conducted as a randomized, double-blind trial. A total of 18 breast cancer patients were enrolled and randomly assigned to two groups. The intervention and control groups received VOT/bis in die (Bid) and placebo, respectively, for 4 weeks. All the patients completed the visual analog fatigue scale (VAFS), fatigue severity scale (FSS), and cancer fatigue scale (CFS) questionnaires before and after the intervention. The best tablet formulation contained *V. odorata* extract 486 mg, PVPK30 50 mg, lactose 450 mg, Avicel PH102 100 mg, SiO_2 14 mg, and magnesium stearate 20 mg. Dimensions, disintegration time, hardness, friability, weight, and total phenolics as pyrogallol were 7.1×9.9×20.3 mm, 28 min, 9.5 kp, 0.37%, 1120mg, 22.8 mg/tab, respectively. More than 80% of the phenolics in the tablets were dissolved during the dissolution test in 30 min. In the pilot study, only VOT treatment significantly decreased the VAFS ($p = 0.02$), FSS ($p = 0.08$), and CFS ($p=0.03$) scores. The results indicated desirable VOT physicochemical characteristics and suggested it as an herbal product for managing CRF in breast cancer patients.

Keywords: *Viola odorata*; Formulation; Breast cancer; Cancer-related fatigue; Pilot study

http://doi.org/10.18502/tim.v10i3.19759

Citation: Heidarirad G, Hajimehdipoor H, Rajabi S, Kashafroodi H, Khancherli F, Malekzadeh Moghani M, et al. **Formulation of *Viola odorata* L. Tablet and Evaluation of the Product Effect on Breast Cancer-Related Fatigue: A Randomized, Controlled Pilot Trial.** Trad Integr Med 2025;10(3): 258-266. http://doi.org/10.18502/tim.v10i3.19759

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Introduction

Fatigue is a complex physiological phenomenon that significantly decreases mental or physical ability [1]. This phenomenon may develop due to sleep disorder, prolonged wakefulness, overwhelming workload, or disrupted circadian rhythm [2]. Regardless of the main cause of fatigue, it can be classified as acute or chronic [3]. Cancer patients may generally experience acute or chronic fatigue during treatment and this may profoundly affect their quality of life [4]. Cancer-related fatigue (CRF) is one of the most common symptoms that may affect 50%-90% of patients with cancer [5]. CRF is completely different from normal tiredness due to its higher severity, higher persistence, and higher debilitating effect on the normal function of the patients than normal fatigue [6]. Several risk factors have been reported for CRF including genetic, biological, psychosocial, and behavioral factors [7]. Several pathophysiological mechanisms have been reported to be involved in CRF, including central toxicity in the nervous system, anemia, neurophysiologic alterations in muscles, inflammatory processes, chronic stress, hormonal imbalances, and sleep deprivation [8]. According to the results obtained from the neuroimmune research era, it has been hypothesized that CRF is driven by the activation of a complex network of pro-inflammatory cytokines [9]. Breast cancer patients who undergo radiotherapy may commonly experience fatigue, which is increased during radiotherapy. Patients who have longer courses of treatment may usually face higher levels of fatigue [10].

A number of treatment strategies have been reported to alleviate CRF including physical activity practices, psychosocial interventions, and mind-body therapies [11]. Medicinal plants have been shown as potential alternative remedies for the treatment of various diseases, and their use is increasingly common around the world [12]. *Viola odorata* L., commonly known as sweet violet, has been traditionally used for the treatment of several diseases such as insomnia, cough, fever, common cold, and headache [13]. This plant contains several compounds, including glycosides, saponins, alkaloids, methyl salicylate, mucilage, and phenolic compounds [14]. In our previous study, aqueous and ethanol extracts of *V. odorata* showed anti-fatigue activity in a rat model of forced swimming test [15]. Therefore, in the present study, a tablet form of *V. odorata* was formulated and quality control tests were performed. Moreover, a pilot, randomized, double-blind, placebo-controlled study was conducted to assess the effect of *V. odorata* tablet (VOT) on the management of CRF in patients with breast cancer who were undergoing radiotherapy.

Materials and Methods

Plant material and drug preparation

Viola odorata aerial parts were purchased from the Tehran herbal market and authenticated in the Herbarium of Traditional Medicine and Materia Medica Research Center (code: HMS-581). The aqueous extract of *V. odorata* (AEVO) was prepared by boiling the powder of the plant for 10 min in the water (1:10). The prepared extract was then dried at 70°C and the resulting powder was used to formulate the tablet. Different pharmaceutical excipients including lactose monohydrate, Avicel PH102, PVPK30, SiO_2, and magnesium stearate were used to prepare tablets. Afterward, the best formula was selected. The physical tests were carried out on the prepared tablets and the selected tablets were subjected to physicochemical and microbial quality control assessments including appearance, dimensions, weight variation, friability, disintegration time, hardness, assay of total phenolics, and dissolution behavior according to United States Pharmacopeia (USP) [16]. In addition, an accelerated stability test was performed on the product at 40°C and 75% humidity for six months. Placebo was prepared with the same shape and color as the VOT by using lactose monohydrate (33.11%), Avicel PH102 (19.90%), PVPK30 (6.62%), starch (33.11%), yellow color (0.0013%), Caramel color (6.62%) and magnesium stearate (0.66%).

Total phenolics content of VOT

In order to standardize the tablet, total phenolics as a quality tablet marker were determined in the VOT using the Folin-Ciocalteu method and pyrogallol as standard [17].

Dissolution profile of VOT

The dissolution profile of the tablets was defined using 900 mL water as a medium at 37°C with a paddle apparatus, a speed of 100 rpm. Sampling was performed in 15, 30, 45, and 60 minutes, and released total phenolics as pyrogallol each time were measured [16,18].

Patients

The present study was conducted on breast cancer patients admitted to the oncology clinic of the Shohada-e Tajrish Hospital, Tehran, Iran. The patients were among the women who were referred to the radiotherapy center and had complaints of fatigue. The informed consent was obtained from all patients before the study. Inclusion criteria included diagnosed breast cancer, age between 18-70 years, under radiotherapy, hemoglobin of at least 8 g/dL or hematocrit of at least 30%, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels less than 3 times of the upper limit of normal, normal range of thyroid stimulating hormones (TSH), creatinine less than 2 mg/dL, and bilirubin less than 2 mg/dL. The exclusion criteria were unstable cardiopulmonary diseases, disabling lung diseases, confirmed history of asthma, history of

allergic reactions to *V. odorata* and excipients, uncontrolled pain, severe infection, underlying disease, and the patient's unwillingness to continue treatment.

Study design and sample size estimation

The present investigation was designed as a pilot double-blind randomized placebo-controlled study. This trial investigated the effect of VOT on the management of CRF in patients with breast cancer. Eligible patients were randomly assigned into two groups (intervention and control groups). A sample size of 18 patients (9 patients in the intervention group and 9 in the placebo control group) was considered with a probable withdrawal rate of 20% in each group.

Randomization and blinding

All patients were randomized into intervention and placebo groups. Using statistical software and a simple randomization method, a randomized list was created. Then, the participants were allocated to two parallel groups by the researcher based on the randomization list. A research assistant (who was not implicated in eligibility assessment or patients' inclusion in the study) assigned a specific code to each patient. The allocated drugs were decoded by the research assistant at the end of the study. The research assistant and the participants were blind.

Drug treatment

Each patient in the intervention group received VOT at a dose of one tablet/b.i.d for 4 weeks. The patients in the control group received the placebo. The standard questionnaires and VAS scale were filled by all patients at weeks 0 and 4 of the treatment period. The participants were requested to report any symptoms that they may observe during the interventions. Participants were also informed that they could withdraw from the study upon their request. After 4 weeks, the data were gathered and statistically analyzed.

Outcome measures

In this present trial, the scores of CRF were estimated by recording the visual analog fatigue scale (VAFS), fatigue severity scale (FSS), and cancer fatigue scale (CFS) for breast cancer patients on weeks 0 and 4 of the study. VAFS is a scale consisting of 18 items associated with the subjective experience of fatigue. The VAFS score range is between 0 and 10, where zero indicates no sign of fatigue and 10 shows the most severe form of fatigue. As the second outcome measure, FSS is defined as a self-administered questionnaire consisting of 9 questions that estimate the severity of fatigue in the patient during the past week. Each question can be scored from 1 to 7 by the participant in FSS form, in which score 1 is indicative of strong disagreement and score 7 indicates strong agreement. The CFS form is used to evaluate fatigue scale in cancer patients, in which a 15-item scale consisting of 3 subscales (physical, affective, and cognitive) is included. The secondary outcome in the present study was any reported side effects by patients. In the CFS questionnaire, the scores of questions that measured the energy level and had the opposite score to other questions were reversed by the statistical consultant and then the sum of them was calculated.

Statistical analysis

The results of the present trial were presented as mean ± standard deviation. The comparison between the baseline characteristics was carried out using independent *t*-test. The differences in outcomes between the two groups were analyzed by paired *t*-tests and one-way analysis of covariance (ANOVA) tests. The statistical significance was considered for p values less than 0.05. All data were analyzed using SPSS software version 26 (Chicago, IL, USA).

Ethical considerations

The present study was carried out following the guidelines proposed in the Declaration of Helsinki (2013 revision). This trial was also approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1400.1037). The trial was registered in the Iranian Registry of Clinical Trials with the following code: IRCT20220302054170N1. All patients signed the informed consent form before enrollment in the study.

Results

Tablet formulation

Different formulations of VOT with physical characteristics have been shown in table 1.

In the first step of tablet formulation, the direct-compression method was used. The powdered dry extract was mixed with SiO_2 and magnesium stearate but a sticky tablet was obtained (F1). In order to reduce stickiness, lactose monohydrate was applied (F2-F5) but lactose was unable to omit the adhesive property of the product. In the next step, SiO_2 was increased along with Avicel PH102. However, despite lower stickiness, the compressibility of the powder was decreased and low tablet hardness resulted (F6-F10); therefore, it was decided to use the wet-granulation technique. In F11-F15, lactose was added as an intra- and extra-granular excipient, and less adhesive tablets were produced. Moreover, magnesium stearate was increased for better flowability of the granules. Finally, using intra- and extra-granular lactose and Avicel PH102, a suitable tablet was acquired.

Quality control of VOT

The physicochemical characteristics of VOT are

Table 1. Different formulations of *Viola odorata* tablet (VOT)

No.	Ingredient (mg)						characteristics
	extract	PVP K30[a]	Lactose	Avicel PH102	SiO_2[b]	MgSt[c]	
F1	486	-	-	-	10	10	Sticky tablet
F2	486	-	50	-	10	10	Moderate compressibility Sticky tablet
F3	486	-	100	-	10	10	Moderate compressibility Sticky tablet
F4	486	-	150	-	10	10	Moderate compressibility Sticky tablet
F5	486	-	200	-	10	10	Moderate compressibility Sticky tablet
F6	486	-	300	-	15	15	Moderate compressibility Sticky tablet
F7	486	-	300	50	15	15	Low compressibility Sticky tablet
F8	486	-	300	100	15	15	Low compressibility Sticky tablet
F9	486	-	400	100	15	15	Low compressibility Sticky tablet
F10	486	-	400	150	15	15	Low compressibility Low hardness Sticky tablet low compressibility
F11	486	50	400[d] 100[e]	-	15	15	Low hardness Less stickiness Good hardness
F12	486	50	400[d] 100[e]	-	14	20	Good compressibility Less stickiness Good hardness
F13	486	50	350[d] 150[e]	-	14	20	Good compressibility Less stickiness Good hardness
F14	486	50	400[d] 100[e]	80	14	20	Good compressibility Very low stickiness Good hardness
F15	486	50	350[d] 100[e]	100	14	20	Good compressibility Without stickiness Good hardness Good compressibility

a: PVP K30: Polyvinylpyrrolidone K30; b: SiO_2: colloidal silicon dioxide; c: Magnesium stearate; d: intra-granular; e: extra-granular

shown in Table 2. The total phenolic content of the tablet was determined by using a calibration curve of pyrogallol as standard material ($y = 10.842x + 0.0117$; $R^2 = 0.999$). The dissolution profile of VOT has been demonstrated in Table 3. As is obvious in Table 3, more than 80% of phenolics have been released in 30 min. An accelerated stability test showed the tablets were unstable at 40°C and 75% humidity. They became soft with an undesirable odor but the tablets at room temperature and humidity had suitable physicochemical and microbial characteristics.

Patients' enrollment and exclusion

A total of 18 patients participated in the present pilot study from Shohada-e Tajrish Hospital (2022-2023). All patients were randomized into two control and intervention groups. During the 4-week study, 4 patients (3 patients in each group) were excluded. Fourteen patients completed the trial and were analyzed (7 patients in each group). The CONSORT flowchart of the recruitment, allocation, intervention, follow-up, and analysis for both control and experimental groups has been shown in figure 1.

Baseline clinical data

Baseline characteristics of patients in the experimental and placebo groups have been demonstrated in Table 4. There was no significant difference between baseline characteristics in the two groups ($p>0.05$).

Efficacy

The results of drug efficacy in VOT and placebo control groups have been shown in table 5. According to the results, there was a significant difference between

Table 2. Physicochemical characteristics of *Viola odorata* tablet

Test	Results
Appearance	Brown, oval, biconvex, scored tablet
Length	20.30±0.02 mm
Diameter	9.93±0.02 mm
Thickness	7.06±0.03 mm
Weight	1.0892-1.1290 g
Disintegration time	28:00 min
Hardness	9.51±0.17 kp
Friability	0.37±0.07%
Assay of total phenolics as pyrogallol	22.8±0.21 mg/tab
Dissolution (30 min)	91.2±7.4%

Table 3. Dissolution profile of *Viola odorata* tablet

Tablet no.	Released phenolics%			
	15 min	30 min	45 min	60 min
1	58.9	96.0	102.5	102.9
2	47.3	85.1	100.0	100.3
3	64.0	103.6	108.7	109.1
4	50.9	87.6	102.9	101.4
5	51.7	84.4	101.8	102.5
6	56.4	90.5	96.7	98.9
Mean ± SD	54.9±6.1	91.2±7.4	102.1±3.9	102.5±3.5

Table 4. Baseline characteristics of patients both in the experimental and placebo groups

Variable	Experimental	Placebo	*p* value
Age	47.28 ± 5.28	53.57 ± 11.97	**0.23**
Hemoglobin	12.98 ± 1.10	12.72 ± 1.22	**0.62**
Hematocrit	38.08 ± 2.53	38.70 ± 2.91	**0.91**
TSH[a]	1.08 ± 0.62	1.26 ± 0.97	**0.35**
AST[b]	20.12 ± 4.49	22.14 ± 5.69	**0.56**
ALT[c]	19.53 ± 6.88	21.86 ± 7.78	**0.42**
Creatinine	0.81 ± 0.05	0.91 ± 0.10	**0.81**
Total bilirubin	0.69 ± 0.08	0.70 ± 0.14	**0.66**
Direct bilirubin	0.24 ± 0.08	0.23 ± 0.07	**0.12**

a: TSH: Thyroid stimulating hormone, b: AST: Aspartate aminotransferase, c: ALT: Alanine aminotransferase

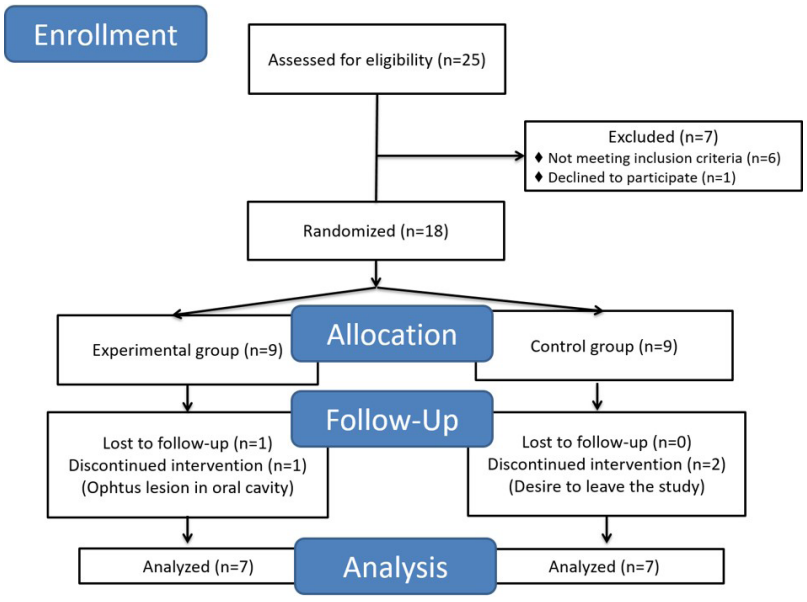

Figure 1. CONSORT flow diagram representing the groups' allocation, enrolment, intervention, follow-up, and analysis in both groups of the study

the VAFS score before and after the intervention (p= 0.01). The statistical analysis of FSS and CFS data revealed a significant decrease in the total score of the FSS and CFS after the intervention (p<0.05). There was no significant difference between the VAFS, FSS, and CFS scores before and after the placebo treatment (p>0.05).

There was no significant difference between the placebo and VOT groups in the VAFS score before the intervention (p=0.2). However, after the intervention, a significant difference was shown between the placebo and VOT groups in the VAFS score (p=0.02). No remarkable difference was observed between the placebo and VOT groups in the FSS score before (p=0.5) and after the intervention (p=0.08). There was no significant difference between the placebo and VOT groups in the CFS score before the intervention (p=0.9). However, a considerable statistical difference was evidenced between the placebo and VOT groups in the CFS score after the intervention (p=0.03).

Discussion

In the formulation part, due to the adhesive and humectant properties of *V. odorata* extract, resulted tablets were sticky; therefore, it was necessary to use a higher ratio of excipients such as lactose and SiO_2. Colloidal silicon dioxide is one of the excipients which is widely used in pharmaceutical products. Its small particle size and large specific area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in the formulation process. It is a tablet disintegrator, as well [19]. Despite increasing excipients, the adhesive surface of VOT remained unchanged; therefore, the usage of the wet-granulation method was obligated. In this process, lactose was used in different proportions as an intra- and extra-granular excipient. Moreover, Avicel PH102 was also used as an absorbent, anti-adherent, diluent, lubricant, and disintegrator agent. By using the mentioned excipients, the tablet characteristics improved and finally the last one containing *V. odorata* extract 486 mg, PVPK30 50 mg, lactose 450 mg, Avicel PH102 100 mg, SiO_2 14 mg, and magnesium stearate 20 mg was achieved as the best formula. According to the results of the accelerated stability test, VOT are susceptible to high temperature and humidity which should be considered in drug transportation and suitable industrial packaging is necessary [20,21].

The data from the pilot study may indicate that VOT can help breast cancer patients who are under radiotherapy to alleviate their CRF. There is very limited data regarding the anti-fatigue activity of *V. odorata* in the literature. For example, in our previous study on the anti-fatigue effects of *V. odorata* in a rat model of fatigue using a forced swimming test, it was shown that both ethanolic and aqueous extracts of *V. odorata* significantly increased the forced swimming time of the rats treated with these extracts. The different plant extracts significantly increased serum glucose levels; while decreasing serum lactate dehydrogenase (LDH). The ethanolic extract of the plant increased serum levels of tumor necrosis factor-α (TNF-α); however, the aqueous extract did not affect TNF-α levels. Further histopathological analyses on the liver tissues of the experimental rats revealed no hepatotoxicity within aqueous extract groups in comparison to the ethanolic extract-treated rats, suggesting the lack of toxicity of the plant water extract [15]. The safety profile of the plant has been reported in two previous investigations. In a study conducted by Siddiqi and his colleagues to unravel the acute toxicity of *V. odorata* in BALB/c mice, increasing oral doses of plant leaf extract (1, 3, and 5 g/kg of body weights) were administered to the mice. The findings showed that there was no death, slow movement, or aggressive behavior in the mice, and the mice were still active 48 hours after the drug treatment [14]. In the other study by Vishal, et al, the

Table 5. Mean outcome measure scores between the two groups of the study before and after the study

Outcome measure		VOT[d] (n = 7)	Placebo (n = 7)	p value
VAFS[a] score	Before	5.71 ± 1.60	4.71 ± 1.11	p = 0.2
	After	2.42 ± 1.98	4.85 ± 1.46	p = 0.02
		p = 0.01	p = 0.73	
FSS[b] score	Before	35.28 ± 11.61	32.28 ± 6.77	p = 0.5
	After	20.85 ± 14.12	31.71 ± 5.25	p = 0.08
		p = 0.004	p = 0.86	
CFS[c] score	Before	44.57 ± 6.24	44.42 ± 4.85	p = 0.9
	After	34.71 ± 9.32	45.28 ± 7.27	p = 0.03
		p = 0.01	p = 0.66	

[a]: VAFS: Visual Analogue Fatigue Scale, [b]: FSS: Fatigue Severity Scale, [c]: CFS: Cancer Fatigue Scale, [d]: VOT: *Viola odorata* tablet

healthy rats were divided into two groups (5 rats in each group). The test group received an acute dose of the crude extract of *V. odorata* plant (2000 mg/kg); while the control group received only 1% Tween 80 in water. The results of that study proved that within 24 hours after the administration of the extract at a dose level of 2000 mg/kg, no lethal effects and mortality were observed among the animals [22].

Immunomodulatory effects of *V. odorata* have been reported in several studies. Dayani, et al demonstrated that *V. odorata* exerts anti-inflammatory effects on a mice model of multiple sclerosis by modulating the levels of pro-inflammatory cytokines. They asserted that this immunomodulatory effect of *V. odorata* comes from cyclotides isolated from the plant [23]. Fallah, et al. revealed that *V. odorata* significantly reduced the levels of interleukins 4, 5, and 13 in bronchoalveolar lavage fluid of asthmatic mice. This plant also decreased hyperplasia of goblet and lymphoid tissue along with the peribronchial and perivascular inflammations in lung tissues [24]. In another study, treatment of a mouse model of neuroinflammtory disease with *V. odorata* significantly decreased inflammatory biomarkers nuclear factor kappa B (NF-κB), TNF-α, and Cyclooxygenase-2 (COX-2) [25]. Several lines of evidence have shown that inflammatory processes play a pivotal role in fatigue induction. For example, pro-inflammatory cytokines have a specific ability to act on the central nervous system leading to some behavioral changes such as fatigue development [26]. Moreover, any changes in the inflammatory responses in patients with cancer, multiple sclerosis, or diabetes are associated with high rates of fatigue [27-29]. It has been demonstrated that radiotherapy augments the success of therapy at all stages of breast cancer [30]. Nonetheless, the patients who undergo radiotherapy may suffer from several adverse effects, such as nausea, vomiting, hair loss, anxiety, skin changes, and fatigue [31-33]. The clinical reports have shown that fatigue is the most common complaint of breast cancer patients who receive radiotherapy [34]. Radiotherapy has been numerously reported to induce inflammatory responses in cancer patients [35-38]. Therefore, it may be implied that radiotherapy-induced inflammatory processes could serve as one of the important mechanisms of fatigue development in cancer patients who receive radiation therapy. This can further suggest that anti-inflammatory compounds may act as potential complementary and add-on therapy to relieve fatigue in cancer patients. Anti-fatigue effect of VOT in the present study may arise from its anti-inflammatory activity.

Another possible underlying mechanism of anti-fatigue activity of VOT may arise from the positive effect of *V. odorata* on the improvement of sleep quality. Karimi, et al conducted a triple-blind randomized clinical trial to investigate the potential effect of *V. odorata* syrup on the management of sleep quality in menopausal women. Their data clarified a significant increase in the Pittsburgh Sleep Quality Index (PSQI) in subjects who received the syrup regularly [39]. In another randomized, double-blind, placebo-controlled clinical trial, the efficacy of *V. odorata* oil in the improvement of sleep quality in patients with chronic insomnia was evaluated. The results of that study highlighted a significant improvement in PSQI and Insomnia Severity Index (ISI) scores in patients who consumed the oil, suggesting the efficacy of this remedy for the improvement of sleep quality in insomniac patients [40]. In a pilot double-blind randomized placebo-controlled clinical study, Shayesteh, et al, studied the effect of *V. odorata* syrup on the sleep quality in patients with depression or obsessive-compulsive disorder (OCD). After 4 weeks, they collected the data and observed that the mean PSQI score was significantly increased in the intervention group as compared with the placebo, suggesting the syrup as a potential adjunctive therapy for the management of sleep disorder in depressed or OCD patients [41]. A systematic review and meta-analysis evaluated the effect of *V. odorata* extract on the management of insomnia. The analysis of PSQI, subjective sleep quality, sleep duration, and ISI scores revealed that *V. odorata* extract may improve sleep quality in patients with chronic insomnia [42].

Limitations

Although the present trial was a pilot study, a major limitation of the study was the small sample size. Therefore, future studies need to use larger sample sizes to prove the effect of VOT on CRF in women with breast cancer undergoing radiotherapy. The other limitation of the study was the evaluation of the patients who received radiotherapy only and no chemotherapeutic agents were received.

Conclusion

The formulated VOT tablet containing lactose, Avicel PH -102, PVP K30, silicon dioxide, and magnesium stearate showed reasonable physicochemical characteristics with appropriate phenolics release behavior. Based on the results of the present pilot study, VOT was a potential efficient herbal remedy to alleviate CRF in breast cancer patients who were undergoing radiotherapy. According to the results of some previous animal studies, VOT did not induce significant side effects. Our observations also revealed no sign of adverse effects in patients who received the drug. However, it is recommended to conduct more comprehensive clinical trials with larger sample sizes and a broad range of experimental tests to affirm the anti-CRF effects of VOT and its underlying mechanisms.

Conflict of Interests

No potential conflict of interest was reported by the author(s).

Acknowledgements
We would like to express our special thanks to the Vice-Chancellor for Research, Shahid Beheshti University of Medical Sciences, Tehran, Iran. This work was supported by the School of Traditional Medicine, Shahid Beheshti University of Medical Sciences with grant number 01-29998.

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