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Comparing the Effect of Dill Seed Vaginal Cream, with a Persian Traditional Base, and 1% Clotrimazole Vaginal Cream on Vulvovaginal Candidiasis: A Double-Blind, Randomized Clinical Trial

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Abstract

Background: Vulvovaginal candidiasis (VVC) is a very common debility in gynecology clinics. Despite access to several antifungal agents, VVC is still a challenge; therefore, presenting a novel antifungal agent, especially with a traditional origin, is of interest and demand.

Objectives: The current study aimed at comparing the efficacy of *Anethum graveolens* L. (dill) vaginal cream with that of 1% Clotrimazole vaginal cream to treat VVC.

Methods: A prospective, single-center, randomized, double-blind clinical trial was performed. In the current study, married females aged 18 - 65 years, with probable vulvovaginal candidiasis were enrolled for primary evaluation. After VVC confirmation by the sniff test, the patients were allocated into three groups with regard to blocked randomization, and inclusion and exclusion criteria. The first group (n = 59) was treated with 1% Clotrimazole vaginal cream; the second (n = 60) with a combination of dill seed essential oil and dried aqueous extract vaginal cream (TEE); and the last (n = 56) with dill seed essential oil vaginal cream (EO) for seven nights. After 10 days, the therapeutic effects were assessed.

Results: After the intervention, itching decreased to 30.5%, 3.3%, and 12.5% in the Clotrimazole, TEE, and EO groups, respectively; the sniff test also decreased to 33.9%, 13.3%, and 12.5%, respectively. Although a statistically significant difference, according to itching and sniff test, was observed among the three groups ($P < 0.001$, $P = 0.005$), there was no significant difference between TEE and EO ($P = 0.06$).

Conclusions: The current study showed that the herbal preparation could be used as an alternative antifungal agent for vulvovaginal Candidiasis.

Keywords: *Anethum graveolens*, Antifungal Agent, Candidiasis, Clotrimazole, Dill Seed, Essential Oil, Herbal Preparation, Traditional Medicine, Vaginal Cream, Vaginitis

1. Background

Vulvovaginal candidiasis (VVC) is one of the most frequent debilities in gynecology clinics (approximately 10 million gynecologic office visits annually in the United States) (1). At least one episode of VVC can be experienced by 75% of all females in fertile age during their lifetime, of whom approximately 50% experience recurrent candidiasis. And almost 5% of infected females are resistant to treatment and spend a refractory period (2) that their quality of life and sexual health are influenced expressively (3, 4).

Candida albicans is known as a normal flora of the genital and gastrointestinal tracts, accounting for 20% to 25% of vaginal discharge culture of asymptomatic females (5). Impairing the balance between *C. albicans*, the resident bacterial flora, and other vaginal defense mechanisms cause *Candida* overgrowth and vaginitis. Although

C. albicans is the most common *Candida* species (about 85% to 90%) causing VVC (1), predominantly non-albicans *Candida* species such as *C. glabrata*, *C. parapsilosis*, *C. kruseiand*, *C. tropicalis*, increasing nowadays, are liable for dose-dependent or resistant candidiasis (6, 7).

The symptoms of VVC including itching, vaginal discharge (commonly thick, adherent, and "Cottage cheese-like"), irritation or discomfort (vulvar burning) and dyspareunia, and signs including vaginal and vulvar erythema and edema (8). Intravaginal imidazoles, Nystatin, Boric acid, and Fluconazole are used for VVC as conventional treatments (5, 9). According to the broad and inappropriate use of antifungal agents (self-medication, prolonged, and empirical use), the prevalence of non-albicans *Candida* species and dose-dependent resistance are increased and infection caused by them have higher minimum inhibitory concentrations (MICs) to the azole antifungal agents, and therefore, resistant to cure (6). Also, predisposing factors such as pregnancy, diabetes mellitus, oral contraception, and consuming systemic antibiotics enhance this infection (10). Serious side effects such as hepatotoxicity and raising the level of hepatic enzymes are reported for ketoconazole and Fluconazole therapy (11-13).

Natural sources can be worthily used to cure infections, which attract many clinical microbiologists and pharmacology companies. Hence, presenting new potent antifungal drugs, especially with a herbal and traditional origin experienced for thousands of years (14) is motivated by factors such as few accessible effective antifungal medicines, drug resistance, expense, and adverse effects (15, 16).

Due to increased global interest in plant research with a traditional origin and their therapeutic potential, using scientific approaches is extremely needed to evaluate their properties, safety, therapeutic effects, and their validity (17-19).

Anethum graveolens L. belonging to family Umbelliferae with common name of dill is an annual aromatic plant originated from the Mediterranean region, as well as Central and Southern Asia and native to Southern Europe. This plant has a broad utilization either as a spice or medicine for a variety of ailments worldwide (20).

Recent in vitro and animal studies demonstrated anti-Candida effects of dill seed essential oil (21, 22). Likewise, investigation of Persian medicine texts demonstrated that dill seed is used as a remedy for vaginitis for many years (23, 24). However, the therapeutic effects of this medicine are not yet examined for vaginal candidiasis in human.

2. Objectives

The current study aimed at comparing the effects of dill seed vaginal cream with those of 1% Clotrimazole vaginal cream to treat vaginal candidiasis.

3. Methods

3.1. Study Design

The current double-blind, randomized clinical trial was conducted to compare the therapeutic effects of 1% Clotrimazole vaginal cream, 2% dill seed total extract vaginal cream (TEE), and 2% dill seed essential oil vaginal cream (EO) on VVC. After obtaining approval from Ethics Committee of Kerman University of Medical Sciences (ethical code: IR.KMU.AH.REC.1395.15, date: 2016-07-13), the study was conducted on 186 patients with VVC referred to the gynecology clinic of Afzalipour state and referral Hospital, affiliated to Kerman University of Medical Sciences, Kerman, Iran, from July 2016 to March 2017; the study was also registered at the Iranian Registry of Clinical Trials (registration code: IRCT2016071929004N1, date: October 2016). The participants were then block-randomized into three groups of 63 patients for Clotrimazole, TEE, and EO.

3.2. Study Population

The inclusion criteria of the participants were married, age range of 18 - 65 years, signs and symptoms of VVC, sniff test confirmation (10% KOH), no pregnancy, lactation, and chronic diseases (e g, kidney, liver, or cardiac failure, and diabetes), lack of immunodeficiency diseases, or complicated VVC based on the gynecologist's diagnosis, not taking immunosuppressive agents or any vaginal drugs during the study, and no consumption of systemic antibiotics and systemic anti-fungal agents four weeks before intervention. The patients with drug therapy complication, pregnancy, menstruation, non-compliance with treatment and the ones with Gardnerella or Trichomonas vaginitis were excluded from the study.

3.3. Sample Size

According to the pilot study parameters and the sample size equation:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}}\sqrt{P(1-P)} + Z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\right)^2}{(P_1-P_2)^2}$$

$P_1 = 0.86$,
$P_2 = 0.63$,
$\alpha = 0.05 \rightarrow Z_{1-\alpha/2} = 1.96$,
$\beta = 0.2 \rightarrow Z_{1-\beta} = 0.8$,

and expected power of 80%, the sample size (n) was estimated 53 patients in each group; 10% - 15% dropouts were also considered and added to the estimated sample size. Therefore, the current study was continued through blocked randomization.

3.4. Data Collection Instruments

Data collection instruments consisted of a socio-demographic questionnaire (including age, education level, and economic status); a daily self-report checklist for vulvar symptoms severity, scored from 0 (no) to 10 (very severe) for each symptom; and also a data collection form to record clinical observations as well as the sniff test (10% KOH). The checklists were competed at baseline and about three days after the intervention. At the end of the study, each variable was analyzed separately. To assess the validity and reliability of the checklist, it was translated into Persian and again back-translated. This checklist has 21 questions. The face validity of the checklist was assessed by five gynecologists in two quantitative and qualitative stages. The impact score was assessed in quantitative stage and all questions were accepted (impact score > 1.5). To validate the content of the checklist, in the qualitative assessment stage, 10 gynecologists assessed the content validity by a focus group. In a quantitative stage, the content validity ratio (CVR) and content validity index (CVI) were assessed and questions with CVR or CVI less than the limit were revised. This process was repeated until obtaining acceptable CVI (> 0.79) and CVR (0.62) values. The test-retest method was performed and Cronbach's alpha was calculated to assess reliability. Cronbach's alpha of the questionnaire for all questions was 0.83. To collect data, a daily self-report checklist was designed for patients.

3.5. Randomization

The patients were randomly divided into three groups of A, B, and C codes through block random allocation with block sizes of three and six, with allocation ratio of 1:1:1. The allocation was performed by an independent expert.

3.6. Preparing Herbal Ingredients of Dill Seed Vaginal Cream

For the current experiment, the herbal samples were prepared from Mahan city, Kerman Province (30.3°N, and 57.0°E), Iran, from May to June 2015, identified by an herbalist with the voucher specimen (KF 1137) and kept in the Herbarium of Pharmacognosy Department, Kerman University of Medical Sciences, Kerman, Iran.

The hydro-distillation method with a Clevenger apparatus was used to provide dill seed essential oil (2% v/w); and its aqueous extract was obtained after filtering the aqueous residue, from hydro-distillation, and dried in room temperature. In the current study, 2% dill seed essential oil (EO) and a combination of 18% dried aqueous extract and 2% essential oil (TEE) were utilized in the form of standardized vaginal formulations (Carvone was identified as the major component of essential oil (55.1%) by GC-MS (gas chromatography-mass spectrometry) library with retention indices 16.85).

3.7. Blinding

Clotrimazole vaginal cream was purchased from Iran Najo Pharmaceutical Co. (Tehran, Iran; registration number 1228032288). After preparing the standardized dill seed vaginal creams in two formulations, under the instruction of a pharmaceutist the three creams were made similar in color, consistency, and shape to the authorized oral one in 50-g tubes. The tubes were sealed and labeled as A, B, and C without any other information by an expert not involved in the study. Also, in order to control microbial and fungal contaminations, all formulations were checked before use.

3.8. Study Intervention

The objectives and method of the investigation were explained to the patients and they were ensured about authors' supervision and confidentiality of their information, and that they would receive complete treatment in case of ineffectiveness or adverse effects of drugs. Then, the informed written consent was taken whether receiving a standard treatment or herbal vaginal cream for their illness. According to blocked randomization, the participants were allocated into one of the three treatment groups: 1% Clotrimazole, TEE, and EO vaginal creams. The patients used one applicator for each of the creams (5 g) every night for a week. Each patient was recommended to apply the cream at least 10 days before menstruation, under hygienic conditions, considering commitment with treatment, and recording the symptoms severity in the daily report checklist. The physical exam was performed by the gynecologist and the author, and the discharge samples were taken for the sniff test on the day 10 and the results were recorded in the vulvovaginal symptom questionnaire. The clinical remission symptoms (itching, burning, vaginal discharge, and dyspareunia), and possible complication during the treatment were recorded in the daily self-report checklist, and then the completed checklists were collected. The acceptable remedy was considered as a negative sniff test and symptoms relief. Moreover, fluconazole capsule was used to complete the treatment if the participants were not completely treated. The physical examination and the sniff test result were recorded in the checklist at the baseline as well as three to four days after completion of the intervention by the gynecologist, and finally, the data were compared.

3.9. Sampling Procedure

After obtaining the history of each patient with VVC complains (itching, vaginal discharge, burning, and dyspareunia) and recording in the checklist, with regards to the inclusion criteria, the patients were examined by the author and the gynecologist for the severity of VVC signs (cheesy white discharge, erythema, and even edema). The discharge samples were taken from the top and side walls of the vagina by a sterile (autoclaved for 15 minutes at 120°C) cotton swab while the patient was placed in lithotomy position. The swab was drawn on a slide, and one or two drops of potassium hydroxide (10% KOH) were added to it and was examined under the microscope (40X magnification) by a pathologist blinded to the study. Observation of budding yeast cells and pseudohyphae confirmed the diagnosis and the results were recorded in the observations checklist. The amine odor due to *Trichomonas* and *Gardenella* vaginitis after adding 10% KOH as an exclusion criterion was considered.

3.10. Study Outcomes

All the participants were visited twice at the baseline and on the day10 after the intervention. The primary outcomes included improvement in VVC symptoms recorded in the checklist.

The analysis of the vaginal discharge samples was performed as the secondary outcome measures on the days 0 and 10.

3.11. Statistical Analysis

SPSS version 20 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The descriptive statistics including mean (standard deviation) and frequency (%) were used to compare the demographic characteristics, clinical manifestations, and laboratory test before and after the intervention. And due to the non-normal distribution of data, nonparametric tests including Chi-square, Wilcoxon signed-rank, the Kruskal-Wallis, the McNemar's and the Shapiro-Wilk tests were used to assess the intervention. Statistically significant level was considered $P < 0.05$.

4. Results

The current study was conducted on 186 females (the Clotrimazole, TEE, and EO groups each of 62 subjects) with vaginal candidiasis. During the investigation, 11 participants (three from the Clotrimazole group, two from TEE, and six from EO groups) were excluded due to pregnancy, incomplete treatment, and allergy. Finally, 175 patients completed the designed protocol. The current study evaluations (clinical evaluations and laboratory tests) were performed at the baseline and about three days after the intervention on the day 10 (Figure 1). The results revealed no significant differences among the three groups in terms of sociodemographic characteristics such as age, education level, economic status, as well as disease conditions (e.g., acute, recurrent (> 4/year) according to Chi-square test ($P > 0.05$) (Table 1). At the baseline, the itching was determined as clinical hallmark with 56%, 68%, and 48% in the Clotrimazole, TEE, and EO groups, respectively, showing no significant difference among them ($P = 0.1$) (Table 2).

Itching decreased in Clotrimazole, TEE, and EO groups from 98.3%, 100%, 100% to 30.5%, 3.3%, and 12.5%, respectively. To better understand the improvement process, the clinical severity of symptoms before and after the intervention are presented as the mean scores for each variable among the three groups in Figure 2.

For symptoms such as itching, burning, vaginal discharge, dyspareunia, and signs such as erythema and edema, all the groups showed significant differences between the baseline and after the intervention using Wilcoxon test ($P < 0.0001$). Although the obtained results showed significant differences with regards to the main clinical symptom (itching) among the three groups ($P < 0.001$), there was no significant difference between TEE and EO groups ($P = 0.06$). Recovery of burning, dyspareunia, and edema were analytically similar to each other among the groups, but significant differences were observed for the other symptoms in the three groups (Table 3).

For all the participants at the baseline, the presence of yeast or mycelia indicated the positivity of the sniff test. After the intervention, sniff test stayed positive for Clotrimazole, TEE, and EO groups: 33.9%, 13.3%, and 12.5%, respectively. The results demonstrated an analytically significant difference both in intergroup and intragroup comparisons after the intervention ($P < 0.0001$, $P = 0.005$).

In EO group, three participants reported burning till the 3rd day, and two reported abdominal pain. In TEE group, one patient reported abdominal pain, one burning, and one headache; however, concerning these complications, there was no statistically significant difference among the study groups ($P > 0.05$).

The results showed a significant difference in remission period of itching among TEE and EO vaginal creams, and Clotrimazole vaginal cream (as the standard treatment) ($P = 0.005$ and $P < 0.001$, respectively), using the Kruskal-Wallis test. In the current evaluation, the highest recovery rate belonged to Clotrimazole group versus TEE group with the lowest recovery rate. But no significant difference was demonstrated between TEE and EO groups ($P = 0.8$).

Table 1. Sociodemographic Characteristics of Participants[a]

	Clo, N = 59	TEE, N = 60	EO, N = 56	P Value
Age, y	35.34 ± 8.82	33.08 ± 8.71	36.36 ± 9.31	0.1
Condition				0.1
Newly infected	19 (0.32)	8 (0.13)	12 (0.21)	
Recurrent infection > 4/y	33 (0.56)	44 (0.73)	33 (0.59)	
Persistent infection	7 (0.12)	8 (0.13)	11 (0.20)	
Economic status				0.2
Weak	35 (0.59)	26 (0.44)	31 (0.57)	
Moderate and good	24 (0.41)	33 (0.56)	23 (0.43)	
Education level				0.7
Under diploma	14 (0.24)	11 (0.19)	15 (0.28)	
Diploma	35 (0.59)	35 (0.59)	26 (0.49)	
Academic	10 (0.17)	13 (0.22)	12 (0.23)	

Abbreviations: Clo: Clotrimazole vaginal cream; EO: Dill seed essential oil vaginal cream; TEE: Combination of dill seed essential oil and dried aqueous extract vaginal cream.
[a]Values are expressed as mean ± SD or No. (%).

Table 2. Comparison of Frequency of Symptoms Among Groups at Baseline[a]

Symptom	EO, N = 59	TEE, N = 60	Clo, N = 56	P Value
Itching	35 (0.59)	41 (0.68)	27 (0.48)	0.1
Discharge	16 (0.27)	18 (0.30)	23 (0.41)	
Burning and dyspareunia	8 (0.14)	1 (0.02)	6 (0.11)	

Abbreviations: Clo: Clotrimazole vaginal cream; EO: Dill seed essential oil vaginal cream; TEE: Combination of dill seed essential oil and dried aqueous extract vaginal cream.
[a]Values are expressed or No. (%).

5. Discussion

The current study aimed at clinically evaluating the antifungal effects of dill seed vaginal cream on VVC. In traditional Persian medicine (TPM), this herb was used as a remedy due to its analgesic and antispasmodic properties in gastrointestinal conditions, and as an antibiotic for genital tract infections. Nowadays, many properties of this herb are justifiable by identified components such as phenolics and flavonoids (21, 23, 25).

The mean ages of the patients in the current study were 35.34, 33.08, and 36.36 years for Clotrimazole, TEE, and EO groups, respectively, without a significant difference similar to the results of the study by Bahadoran et al. (26). Among the clinical manifestations, itching was the most prominent hallmark and had the highest frequency in the three groups compared with other studies and gynecology references (8, 27). The comparison between antifungal effects of dill seed vaginal creams and those of Clotrimazole on both clinical manifestations and laboratory test revealed the antifungal efficacy of this herbal medicine (Wilcoxon, $P < 0.05$) with its dominance in some parameters such as itching, discharge, erythema, and remission period compared with Clotrimazole cream (the Kruskal-Wallis test, $P < 0.001$). But, in this respect, there was no significant difference between TEE and EO creams (Bonferroni correction, $P = 0.06 > 0.0167$). Although this difference was not significant, clinically, the participants better tolerated TEE, which was in line with those of the Persian medicine principles (23). At the end of the current study, sniff test was positive for 33.9%, 13.3%, and 12.5% in Clotrimazole, TEE, and EO groups, respectively, which showed recovery rates of 66.1%, 86.7%, and 87.5% for Clotrimazole, TEE, and EO groups, respectively. But in a study performed by Fouladi et al. the recovery rates for *Z. multiflora* and Clotrimazole were 54.3% and 47.4%, respectively. In contrast, in a study by Simbar et al. *Z. multiflora* could not palliate itching compared with Clotrimazole in VVC (28). The differences between the recovery rates may be due to various dosages of the effective substance, the impact of ecological conditions on herbal compositions (20), or even due to personal differences or disease conditions (new, recurrent, or persis-

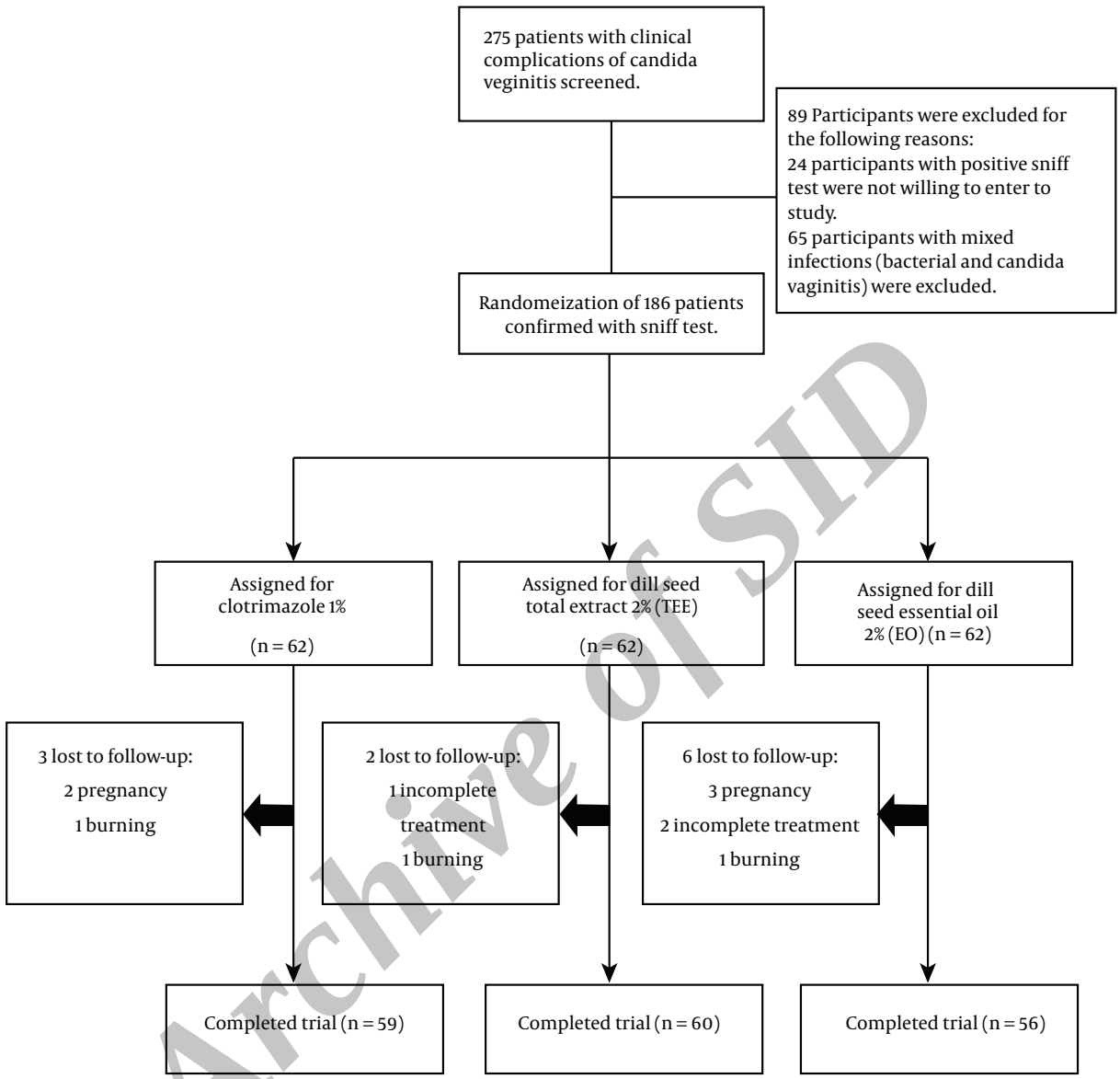

Figure 1. Flowchart of the trial comparing the efficacy of two formulations of dill seed vaginal cream (TEE, EO) with that of Clotrimazole in VVC treatment. TEE, combination of dill seed essential oil and dried aqueous extract vaginal cream; EO, dill seed essential oil vaginal cream; VVC, vulvovaginal candidiasis.

tent infections) that are not determined in most studies.

The main detected component of dill seed essential oil are carvone, limonene, apiol, and α-phellandrene with proven antibacterial, antifungal, antioxidant, insecticidal, and anti-inflammatory properties (29, 30). Naseri et al. showed the remarkable anti-inflammatory effect of dill seed oil, based on the PTM, on rat's paw inflammation compared with diclofenac, which might be attributed to carvone and limonene components (31); congruent with those of the current study results in this regard.

According to the PTM, dill seed is used to cure leucorrhea in ancient dosage forms (decoction for oral consumption, vaginal douching, or in combination with other plants in the form of vaginal suppository) for thousand years (23). Zeng et al. investigated the in vitro and in vivo effects of dill seed essential oil on various candida strains. Their study demonstrated that dill seed essential oil (2% v/v) had a lower value of MIC than that of fluconazole; and also in both prophylaxis and therapeutic purposes, it was more effective than fluconazole in im-

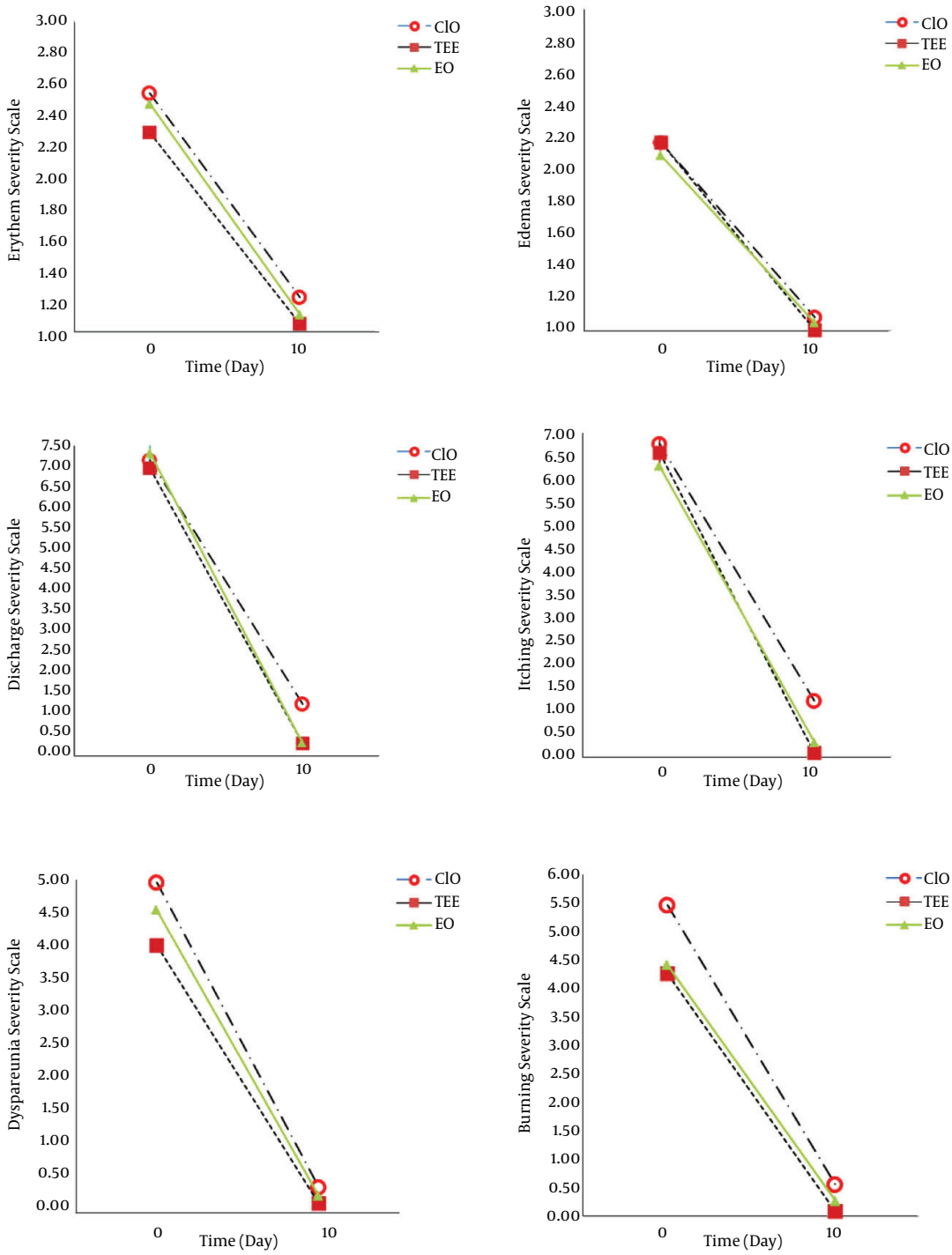

Figure 2. Comparison of the mean severity scores of clinical manifestation at baseline and 10 days after the intervention among the three groups. Clo, Clotrimazole vaginal cream, TEE, Combination of dill seed essential oil and dried aqueous extract vaginal cream, EO, Dill seed essential oil vaginal cream.

Table 3. Inter-and Intragroup Comparisons for Laboratory Results, and Signs and Symptoms at Baseline and 10 Days After Intervention

Clinical Index	Baseline	After Intervention	P Value[a]	P Value[b]	P Value[c]
Itching				< 0.001	0.4
Clotrimazole	58 (98.3)	18 (30.5)	< 0.0001		
TEE	60 (100)	2 (3.3)	< 0.0001		
EO	56 (100)	7 (12.5)	< 0.0001		
Burning				0.07	0.1
Clotrimazole	56 (94.9)	9 (15.3)	< 0.0001		
TEE	46 (76.7)	2 (3.3)	< 0.0001		
EO	42 (75)	7 (12.5)	< 0.0001		
Discharge				< 0.001	0.6
Clotrimazole	58 (98.3)	19 (32.2)	< 0.0001		
TEE	59 (98.3)	5 (8.3)	< 0.0001		
EO	55 (98.2)	7 (12.5)	< 0.0001		
Dyspareunia				0.7	0.3
Clotrimazole	44 (74.6)	5 (8.5)	< 0.0001		
TEE	36 (60)	3 (5)	< 0.0001		
EO	40 (71.4)	5 (8.9)	< 0.0001		
Erythema				0.04	0.1
Clotrimazole	58 (98.3)	12 (20. 3)	< 0.0001		
TEE	58 (96.7)	3 (5)	< 0.0001		
EO	53 (94.6)	5 (8.9)	< 0.0001		
Edema				0.09	0.6
Clotrimazole	53 (89.8)	5 (8.5)	< 0.0001		
TEE	58 (96.7)	0	< 0.0001		
EO	52 (92.9)	3 (5.4)	< 0.0001		
Sniff test				0.005	
Clotrimazole	59 (100)	20 (33.9)	< 0.001		
TEE	60 (100)	8 (13.3)	< 0.001		
EO	56 (100)	7 (12.5)	< 0.001		
The mean remission period of itching				0.005	
Clotrimazole	105.10				
TEE	77.85				
EO	80.86				

Abbreviations: EO, dill seed essential oil vaginal cream; TEE, Combination of dill seed essential oil and dried aqueous extract.
[a] P value before and after intervention for each group (the Wilcoxon test).
[b] P value after intervention among groups (the Kruskal-Wallis test).
[c] P value before intervention.

munosuppressed mice (22).Therefore, with regard to the obtained percentage of dill seed essential oil and TPM prescription (23), this dosage (2%) was selected for the assessment.

To the best of authors' knowledge, for the first time, the current study evaluated the antifungal effects of dill seed vaginal cream compared with those of 1% Clotrimazole vaginal cream on VVC in human beings.

However, a recent study with a smaller sample size compared the efficacy of dill vaginal suppository and Clotrimazole vaginal tablet. The prevalence percentages of itching, leucorrhoea, burning, and positive cultures were

20%, 23.3%, 23.3%, and 10%, respectively for dill suppository, and 16.7%, 20%, 10%, and 13.3% for Clotrimazole tablet at the end of intervention without any significant differences (32).

Bingxin et al. studied the probable antifungal mechanism of dill seed essential oil and revealed its antifungal activity. Lipophilic property of dill seed essential oil facilitates its absorption by fungal mycelia. By affecting plasma membrane and mitochondria, each of the limonene and carvone alone showed antifungal effects, but, when combined together, they were more forceful (29).

Strong points of the current study were as follows: using formulated, standardized herbal antifungal cream including both aqueous extract and essential oil based on PTM texts (24); comparison of this herbal cream with standard treatment and vaginal cream containing only essential oil; applying a herbal medicine based on its worldwide interest (33); and also determining the frequency of disease conditions, by increasing the accuracy of the result interpretation compared to those of most of the other studies (26, 27). Furthermore, utilizing the current dosage form with standardized and reproducible characteristics (34), instead of the ancient dosage form (douching: *abzan*) decreased dropouts due to comfortable usage. Moreover, the current study is regarded as a scientific evidence for traditional medicine research. However, no serious side effects of this herb are reported yet (35), eliminating enterohepatic cycle due to topical usage versus oral consumption may be acceptable for the first step.

Although the current study had some weak points including lack of follow-up evaluations due to time limit, probably small sample size to determine other aspects such as eventual side effects and cases not responding to treatment, using a single dosage of the drug, and lack of placebo group. Hence, it can be suggested that further studies be conducted with different dosage, a bigger sample size or even with oral dosage form (decoction) for probably eradiating gastrointestinal Candida and reducing recurrent infection (11, 36) and also following-up after treatment for a period of time. Due to demonstrating several effects such as antifungal, anti-bacterial, and anti-inflammatory activities of dill seed in recent studies (25, 37) using this formulation to treat both fungal and bacterial vaginitis in future studies can be suggested.

5.1. Conclusion

In conclusion, dill seed vaginal cream can be used as an alternative treatment for vaginal candidiasis; furthermore, it seems to confirm its traditional usage for vaginitis.

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Footnotes

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