Original Article

Comparing the Effectiveness of *Arnebia euchroma* with ClotrimazoleVaginal Cream for the Treatment of Vulvovaginal Candidiasis: A Randomized Controlled Triple-Blind Trial

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Abstract

Background: Vulvovaginal candidiasis is the second most common cause of vulvovaginal infections. Due to the increasing resistance to synthetic antifungal drugs, the use of drugs with a natural origin is a priority. The aim of the present study was to compare the effectiveness of *Arnebia euchroma* with vaginal cream clotrimazole 1% United States Pharmacopeia (USP) for the treatment of vulvovaginal candidiasis**. Materials and Methods:** This triple-blind trial study was performed on 112 women with diagnosed Candida vaginitis clinically and by a laboratory test, patients were randomly divided into two groups receiving *Arnebia euchroma* and vaginal clotrimazole (56 people per group) in clinics and medical centers Ahvaz (Iran) from April 2018 to April 2019. Clinical and laboratory symptoms were recorded at the beginning of the study and 1 week after the end of treatment by a researcher-made questionnaire. Data analysis were performed using SPSS software v-23. $p < 0.05$ was considered significant**. Results:** After the intervention, vaginal culture was negative in terms of Candida in 17 (36.17%) patients of the *Amoeba euchroma* group and 37 (69.81%) patients of the clotrimazole group. The Chi-square showed that there was a significant difference between the culture results in both groups ($\chi^2 = 10.10$, df = 1, $p = 0.001$). No differences were observed between the two groups in terms of vaginal symptoms based on adjustment for age and using a logistic regression model. **Conclusions:** A vaginal cream containing *Arnebia euchroma* could reduce the complaints of vulvovaginal candidiasis. But, future studies with larger sample sizes and different dosages are recommended.

Keywords: *Clotrimazole, Iran, randomized controlled trial, Candidiasis, Vulvovaginal*

Introduction

Vulvovaginal candidiasis is the second most common vaginal infection and is caused by *Candida albicans* in 80% to 85% of cases[1] and 40% to 45% with recurrence.[2] Factors that increase susceptibility to vulvovaginitis candidiasis include antibiotic therapy, pregnancy, uncontrolled diabetes mellitus, oral contraceptives (especially high-dose formulations), immunosuppressants, and artificial clothing.[3] The most important manifestation of vaginal candidiasis is vulvar and vaginal itching. They return and 5% to 8% of women suffer from recurrent candidiasis infections during their lifetime.[4]

Azole antifungals are used to treat vulvovaginal candidiasis.[5] The most common of these drugs are clotrimazole, followed by miconazole, ketoconazole, and fluconazole.[6] However, when infectious species such as *Candida krusei* and some *Candida* species are resistant, other options for this treatment should be considered.[7] A number of treatment options have been proposed, including nonsteroidal anti-inflammatory drugs, plant extracts, and agents that act on biofilms or other fungicidal agents, or even those that are directly fungicidal or antifungal.[8] These options include products that reduce the population of the infectious agent, restore the microbiota balance, restore the pH and increase the population again by lactobacilli, relieve the signs and symptoms, or even eliminate the infection.[9]

Arnebia euchroma is from the family Boraginaceae. This plant has an herbaceous appearance and is covered with sharp silver

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hairs native to southeastern Iran.[10] Studies have shown that the roots of Borage species, including Abu-Khalsa, are rich in naphthoquinone, shikonin, and alkanin.[11] They have internal materials and a wide range of biological abilities such as wound healing, antifungal activity,[12] antiviral, anti-inflammatory, and antimicrobial.[13,14] An *in vitro* study showed the antifungal effects of various extracts of aerial parts and Borage root (in all concentrations) on both *Candida glabrata* and *Candida tropicalis* species.[15] Another study showed that different extracts of Borage root have more antifungal activity than *Candida albicans* on the aerial part.[16] Also, the methanolic extract of this plant has good antifungal effects on *Aspergillus flavus*, *Fusarium moniliform*, and *Aspergillus* accuracy.[17]

Due to the increasing prevalence of opportunistic fungi in susceptible, increased resistance to current antifungal drugs (due to self-diagnosis and self-medication with over-the-counter antifungal drugs), side effects of chemical drugs, increased use of anti-*Candida* plants in recent years the present study,[18-20] and that the effect of purifying the root of the Abu-Khalsa plant on *Candida albicans* has only been studied *in vitro*, and not in clinical settings, the aim of this study is to evaluate the effectiveness of vaginal cream of *Arnebia euchroma* root in women with vulvovaginal candidiasis in comparison with vaginal clotrimazole.

Materials and Methods

This three-blind clinical trial (IRCT20181007041267N1) was conducted from April 2018 to April 2019. The study population included 112 women with positive culture and clinical signs vulvovaginal candidiasis of whom referred to the clinic of Imam Khomeini Hospital in Ahvaz (Iran). The sample size was calculated 56 participants in each group based on previous studies. By assuming power = 80%, α = 0.05, P1 = 36.90, P2 = 63.04, and dropout rate of 10% in each group.

Enrolled patients were randomly divided into two parallel groups. The random allocation program was prepared using computer randomization in six blocks (those receiving *Arnebia euchroma* and those receiving vaginal clotrimazole 1% United States Pharmacopeia (USP)) in a ratio of 1:1.

Initially, the patient's medical history and complaints were recorded with oral consent. Inclusion criteria consisted of having age between 18 and 45 years, being married, husbands' monogamy, having consisted to participate in the study, having no drug sensitivity, having no sensitivity to clotrimazole, and being literate (both in reading and writing). The exclusion criteria consisted of suffering from chronic diseases, using antibiotics, and corticosteroids in the previous 2 weeks, having menstruation, using oral contraceptives, suffering from ulcers and lumps in the cervix based on observation with a speculum, being pregnant, suffering from severe psychological stress, and having no referral after treatment. Then, the subjects were clinically examined under the complete moral principles.

For the examination, the subjects were placed in a lithotomy position and by placing a disposable speculum without the use of lubricant gel, the condition of the discharge, and symptoms were examined and included in the observation record checklist. Then, using a pH meter paper, the pH of vaginal discharge was determined and recorded in a checklist. After that, the vaginal discharge was sampled with three sterile cotton swabs. The first swap was transferred to the slide by adding a drop of normal saline and examined under a Nikon microscope.

To examine the discharge for fungal infection, 10% potassium hydroxide was added to the second slide and a second swab was applied. Both slides were examined under a microscope with magnifications of 10× and 40×, and if key cells and flagellate parasites were seen, they were excluded from the study with an appropriate diagnosis of *Gardnerella vaginalis* and *Trichomonas* infection. If mycelium was observed, the subjects' Candida vaginitis was considered positive. To confirm the results, Gram staining was performed. If Gram staining confirmed the observations under a microscope, a culture sample was prepared for them. Confirming the fungal infection in the Sabouraud Dextrose Agar (SDA) growth medium, as a definite sample, the subjects were contacted by telephone to go to the clinic to receive the medicine. Vaginal cream was prepared under the supervision of a pharmacognosist in the laboratory of medicinal plants of the Shahid Beheshti University of Medical Sciences. The root of *Arneiba euchroma* in the family Boraginaceae was purchased from the pharmaceutical market (reputable perfumers) in Tehran. After ensuring its freshness and identity, it was completely dried in the shade and warmth of the laboratory environment (to prevent bacterial or fungal contamination). After ensuring their complete dryness, it was pulverized with an electric mill and extracted with ethyl alcohol (ethanol) 96% via the maceration method three times. The root powder was poured in a 2-L Erlenmeyer flask and a solvent was poured over it so that it could be covered.

After 24 h in a closed laboratory environment, the supernatant was filtered through filter paper and fresh solvent (ethanol solution 96%) was poured onto the remaining pulp, which still contained active ingredients, and waited again for 24 h. The extracts were mixed three times and evaporated at a temperature below 43°C (in an oven to prevent degradation of the active ingredients of the plant). Finally, a concentrated extract of the plant was obtained. The initial amount of the plant was 500 g, which after extraction with a concentration of 10% of the resulting amount was 50 g of the plant, of which 0.50 g of the plant (as a gram) was inserted into the base of the vaginal cream and mixed thoroughly with it. After ensuring

the uniformity of the product, the prepared vaginal cream was filled in 50 g tubes.

Vaginal cream clotrimazole 1% was prepared by the Pars Darou Company and was provided to the researcher with tubes similar to *Arneiba euchroma* cream with the supervision of pharmacognosists and titled A and B. The sequence of allocation and preparation of envelopes was performed by a third party not involved in sampling and clinical and laboratory examinations. Thus, for each participant, an envelope containing the drug and seven applicators were given. Each participant was also given a pamphlet that taught them how to take medication, nutritional advice, avoid intercourse during treatment as much as possible, and use a condom if they were close and had health tips. To ensure the regular use of drugs, each patient was given a form to fill in after each use of the drug and take it with them each time they visit. Individuals were asked to take one applicator (equivalent to 5 g) of medication per night for 7 nights while sleeping. The subjects were re-examined 4 days after starting the drug to evaluate the possible side effects and patients' compliance with hygiene instructions, 1 week after the end of treatment, they were evaluated for the treatment of the symptoms of Candida vaginitis. The subjects were advised to observe hygienic issues during this period and not to use vaginal douches and other vaginal creams as well as herbal and systemic medicines. Also, they were asked to avoid wearing tight pants during this period. One week after the end of treatment, the subjects were resmeared and microscopically evaluated, and recultured.

The subjects who did not use the vaginal cream for more than one night, had the necessity of taking it during the study, had an allergy to the drugs, or were unwilling to cooperate, were excluded from the study. For the demographic and obstetric information questionnaire, an observation checklist (discharge, pruritus, burning, pelvic pain, dyspareunia, and dysuria) was used. The checklist for recording symptoms and observations has been developed by a researcher, which has been compiled based on the study of resources and articles and distributed to 10 faculty members of the Shushtar University of Medical Sciences and has been validated by the content validity method. Symptoms of burning and itching of the vulva, vaginal discharge, burning and pain in the abdomen, and pain during intercourse were compared between the two groups.

The obtained information was entered into the SPSS software v-22 computer program after coding (IBM© Corp., Armonk, NY, USA). To analyze the data, descriptive statistical tests such as mean and standard deviation as well as inferential Chi-squared, independent *t*-test, Fisher's exact test, and McNemar's test were employed. A significant level was considered $p < 0.05$ with a 95% confidence interval.

Ethical considerations

To conduct the research, written permission was obtained from the ethics committee of the Shushtar University of Medical Sciences under the number IR.SHOUSHTAR.REC.96.01. The researcher after introducing herself to the research units and explaining the goals and information required about the research process, the researcher received written consent from eligible individuals who were willing to participate in the research. The subjects were assured that their information would remain confidential and that they would have the right to withdraw at any stage of the research, and that they would immediately notify the research team of any side effects while taking the drug.

Results

Among 825 women with vaginal complaints, 613 individuals did not meet the inclusion criteria because pH was below 4 and above 4.5, the existence of a wound in the cervix, normal discharge on examination, existence of other infections, pregnancy, diabetes, and IUD. Finally, 112 patients with a positive culture and clinical signs were randomly divided into *Arnebia euchroma* and clotrimazole groups. During the study, 12 participants (9 from the *Arnebia euchroma* group and 3 from clotrimazole group) were excluded due to the distance of the patient's residence from the study site and unwillingness to continue treatment [Figure 1].

The mean(SD) age and standard deviation of the research units in the *Arnebia euchroma* and clotrimazole groups were 38.17 (8.14) and 37.73 (9.43) years, respectively. Independent *t*-test showed there was a significant difference between the two groups. By adjusting the effect of age and using a logistic regression model, the comparison of symptoms after the intervention was performed. No significant difference was found between the two groups in terms of quantitative demographic parameters such as education, occupation, medical records, surgical records, and Body Mass Index (BMI) [Table 1].

The most common complaints of patients before treatment were vulvovaginal itching, vulvovaginal irritation, and vaginal Candida discharge, respectively. No differences were observed between the two groups in terms of vaginal symptoms based on the Chi-square test except for Candidal discharge ($p = 0.004$). Candidates' discharge was compared after the intervention by adjusting the effect of age and status of candidates' discharge before the intervention and using a logistic regression model. In both groups, there was an improvement in symptoms compared with baseline, but by adjusting the effect of age and using a logistic regression model, no statistically significant difference was observed between the two groups [Table 2].

After the intervention, vaginal culture was negative in terms of Candida in 17 (36.17%) patients of the *Arnebia euchroma* group and 37 (69.81%) patients in

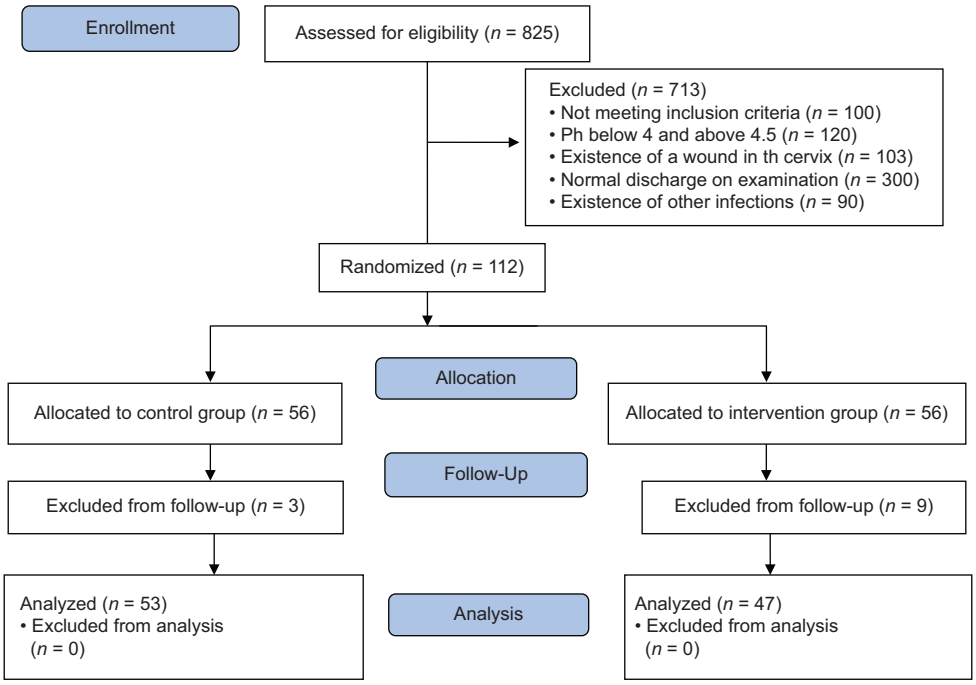

Figure 1: Consort diagram

Table 1: Demographic characteristic of patients in Arnebia euchroma and clotrimazole groups' variables

Qualitative Variables	Intervention (47) *n* (%)	Control (53) *n* (%)	χ^2	df	*p*
Education					
Primary	4 (8.51)	5 (9.45)			0.272
Guidance	12 (25.53)	7 (13.20)	3.90	3	
High school	22 (46.80)	34 (64.15)			
University	9 (19.16)	7 (13.20)			
Job					
Housewife	43 (91.50)	44 (83)	1.58	1	0.246
Employed	4 (8.50)	9 (17)	1.60		
History of vulvovaginal candidiasis candidal vaginitis					
Yes	29 (61.70)	26 (49)		1	0.231
No	18 (38.30)	21 (51)			
Method of contraception					
LD*	13 (27.66)	9 (16.98)	4.91	4	0.296
DMPA**	2 (4.26)	7 (13.20)			
Condom	13 (27.66)	18 (33.96)			
Tubectomy ligament	1 (2.13)	3 (5.66)			
Withdrawal	18 (38.29)	16 (30.20)			
Quantitative Variables	**Mean (SD)**	**Mean (SD)**	***t***	**df**	***p***
Age (year)	31.87 (8.14)	37.73 (9.43)	−3.29	98	0.001
BMI (kg/m^2)***	26.27 (7.52)	25.56 (6.73)	0.57	98	0.570

*Contraceptive low dose (Ethinyl Estradiol + Levonorgestrel). **Depot Medroxy Progesterone Acetate, ***Body Mass Index

clotrimazole group. The Chi-square showed that there was a significant difference between the culture results in both groups [χ^2 = 10.10, df = 1, p = 0.001] [Table 3]. No side effects were reported in the two treatment groups.

Discussion

The results of the current study indicated improvement in vaginitis signs, which was observed in both groups with no statistical difference. Based on the literature review, this is the first clinical study on the effect of *Arnebia euchroma* cream on the treatment of vulvovaginal Candidiasis, but various laboratory studies have shown the effectiveness of different parts of this plant (roots and aerial parts) on reducing fungal growth.[15,21] So comparisons are made with plant studies of this group or with plants with similar active ingredients. Other herbal preparations such as honey,[2]

Table 2: Differences between Arnebia euchroma and clotrimazole groups in their effects on symptoms

Group Symptom	Before treatment			After treatment				
	Intervention (56) *n* (%)	Control (56) *n* (%)	*p*	Intervention (47) *n* (%)	Control (53) *n* (%)	chi-square (χ^2)	df	*p*
Burning vulva and vagina	41 (73.21)	50 (89.28)	0.299	4 (8.51)	9 (16.98)	0.10	1	0.743
Pruritus vulva and vagina	56 (100)	52 (92.85)	1	10 (21.27)	0 (0)	0	1	0.997
Discharge	40 (71.42)	53 (94.64)	0.004	12 (25.53)	5 (9.43)	0.86	1	0.352
Dysuria	23 (41.07)	27 (48.21)	1	0 (0)	5 (9.43)	0	1	0.997
Under abdominal pain	20 (35.71)	30 (53.57)	0.229	2 (4.25)	5 (9.43)	0.74	1	0.387
Dyspareunia	15 (26.78)	10 (17.85)	0.167	5 (10.63)	3 (5.66)	0.31	1	0.572

Table 3: Differences between Arnebia euchroma and clotrimazole groups in laboratory result

Laboratory result	Intervention (47) *n* (%)	Control (53) *n* (%)	χ^2	df	*p*
Result of direct observation under a microscope and culture					
Positive	30 (63.82)	16 (30.18)	10.10	1	0.001
Negative	17 (36.17)	37 (69.81)			

garlic,[22] cinnamon,[23] *Salvia officinalis*,[24] and *Calendula officinalis*[25] have also been clinically evaluated for their effectiveness in vulvovaginal candidiasis symptoms in comparison with clotrimazole.

The obtained results indicate that reduction sign of burning vaginal/vulvar irritation and dysuria was greater in the *Arnebia euchroma* group than in the clotrimazole group. The anti-inflammatory properties of *Arnebia euchroma* can be attributed to the large amounts of phenolic compounds, shikonin, alkanin, flavones, and flavonoids in the root of the *Arnebia euchroma*.[26] Flavonoids prevent the release of histamine and the production of prostaglandins, which cause tenderness, pain, and swelling, and treat redness and pain.[25] Pirbalouti *et al*.,[27] and Mohsenikia *et al*.,[28] showed that an *Arnebia euchroma* extract has beneficial effects in accelerating the healing process of skin wounds in rats. Studies by Hosseini *et al*.,[29] showed that sickening and alkanin (from the active ingredients of *Arnebia euchroma*), as the most important constituents of the plant, have a high ability to reduce inflammation. Ashkani-Esfahani *et al*.,[30] showed that hydroxy naphthoquinone, an important active compound in the root of this plant, has a great ability to relieve inflammation. Considering the progress of the inflammatory process following the increase in peroxidation production, as well as the role of superoxide dismutase, catalase, and glutathione peroxidase of the root of the *Arabia euchroma* plant,[31] it seems logical that the extract of this plant can reduce inflammation. The antifungal properties of hawthorn cream can be attributed to the active ingredient naphthoquinones in the hawthorn plant. The antifungal effect of medicinal plants may be due to the destruction of the fungal cell wall and cytoplasmic membrane due to the release of antimicrobial compounds in plants and plant lytic enzymes on fungal cells.[32] Ghasemi *et al*.,[12] in their study showed the antifungal effects of ethanolic and aqueous extracts of Abu-Khalsa root *in vitro* (mean diameter of growth inhibition zone). However, Naieni *et al*., showed that the plants of *Arabia euchroma*, Chamomile (in the family of Asteraceae), Arctium, Achilleamillefolium, Tussilagofarfara, Broadleaf plantain (in the family Plantaginaceae), Cichoriumintybus, and Echiumdo did not have any significant antifungal effects against this type of strain.[33] This can be due to laboratory criteria for confirming any response to treatment and concentration of the active substance, i.e., specific species of *Candida albicans*. The root of the plant Echiumitalicum (in the family Boraginaceae) at a concentration of 5 mg/mL has more antifungal activity against *Candida albicans* than nystatin.[21] The results of the study by Damianakos *et al*.,[34] showed that the *N*-hexane extract of *Arnebia euchroma* callus had more antifungal properties against *Candida glabrata* than *Candida tropicalis*. Hamedi *et al*.,[35] Showed that Borage ointment at a concentration of 1 mg/dL inhibits *Candida albicans*.

Limitations of this study can be systematic safety and physiological differences between the studied units, failure to determine the type of candidiasis, the severity of *Candida* infection, decrease in the number of samples during the study, and failure to refer to some research units for posttreatment culture (despite being independent). Reasons for not referring to the results of treatment (according to the telephonic report of the individuals themselves), not following the symptoms 1 month after treatment. Also, despite the necessary training on how to use the drug and observe the health tips to the research units, the possibility of not following the health tips should be considered. A triple-blind study design, a control group, and randomized block of samples, a new uncomplicated combination of strengths, and the increase in the validity of the present study are considered. Due to the strong anti-inflammatory properties of this drug, it is recommended to study the effect of *Arnebia euchroma* on chronic and recurrent Candidiasis, particularly burning as the most common symptom of the disease.

Conclusion

This three-blind clinical trial study, for the first time in Iran, compared the effectiveness of *Arnebia euchroma* with vaginal cream clotrimazole 1% USP for the treatment of Vulvovaginal candidiasis. Improvement in Vaginitis signs was observed in both groups with no statistical difference. Vaginal cream clotrimazole 1% USP was more effective than the root of *Arnebia euchroma* ointment in culture results negative. Although *Arnebia euchroma* cream has reduced complaints of vulvovaginal candidiasis, further research with larger sample size and different doses are recommended to evaluate the plant's effectiveness in clinical conditions.

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Conflicts of interest

Nothing to declare.

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