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Original article

Quercus Brantii Lindl. Vaginal Douche Versus Clotrimazole on Vaginal Candidiasis

- A Randomized Clinical Trial -

Zeinab Moshfeghy[1,2*], Khadegeh Asadi[2], Marzieh Akbarzadeh[3], Atefeh Zare[2], Tahereh Poordast[4,5], Masoumeh Emamghoreishi[6], Fatemeh S.Najib[4,5], Mehrab Sayadi[7]

[1] Community Based Psychiatric Care Center, Shiraz University of Medical Sciences, Shiraz, Iran
[2] Department of Midwifery, School of Nursing and Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran
[3] Maternal-Fetal Research Center, Department of Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran
[4] Infertility Research Center, Shiraz University of Medical Science, Shiraz, Iran
[5] Department of OB/GYN, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[6] Department of Pharmacology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[7] Cardio-vascular Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Key Words

clotrimazole vaginal cream, extract, *Quercus Brantii* Lindl., *Vaginal Candidiasis*, vaginal douche

Abstract

Objectives: *Vaginal Candidiasis* with an approximate prevalence of 30% is the second cause of vaginal infections. Antifungal azole is the first treatment for *Vaginal Candidiasis*; however, some side effects have been reported for this chemical medicine. Based on the antifungal activity of Inner Stratum of *Quercus Brantii* (*Q. Brantii*), the aim of our study was to compare the effects of vaginal douche of Q. *Brantii* extract and clotrimazole on *vaginal candidiasis* symptoms before and after the treatments, in women.

Methods: 89 non-pregnant women with positive KOH test which is capable of identifying the presence of hyphae and mycelium by adding KOH (10%), and a positive *vaginal candidiasis* culture were randomly divided into two experimental groups, using permuted block randomization method. One group received clotrimazole vaginal cream (1%) and the other group received vaginal douche of *Q. Brantii* extract. Groups were treated for 7 days and KOH tests and cultures were evaluated again. Data were analyzed via chi-square and independent t-test, using SPSS software.

Results: According to the results, there were no significant differences between experimental groups for demographic characteristics like age (p=0.403), BMI (p=0.911), educational levels (p=0.862) and contraceptive methods (p=0.702). Moreover, significant differences were seen in vaginal discharge between the groups after the treatments (P=0.043).

Conclusion: The results suggested that the therapeutic effect of vaginal douche of *Q. Brantii* extract was approximately similar to that of clotrimazole vaginal cream.

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1. Introduction

Vaginal candidiasis is one of the most frequent infections of the female genital tract [1]. *Vaginal candidiasis* is the second most common cause of vaginitis worldwide, after the bacterial infection. The risk of *vaginal candidiasis* for non-pregnant women is approximately 20%, but it increases by 30% during pregnancy [2]. No complete reporting of the number of women involved

*Corresponding Author
Zeinab Moshfeghy. Community Based Psychiatric Care Research Center, Department of Midwifery, School of Nursing and Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran.
Tel: +98-713-647-4256 Fax: +98-713-647-4252
E-mail: zmoshfeghy1385@yahoo.com

in *Candida vaginitis* is available in Iran [3], but according to a study, the prevalence of *vaginal candidiasis* in Iran is between 25% and 45% [4]. The main reasons for the recurrence of *Candida* are not fully understood [5]. Autoimmune diseases, endocrine diseases, diabetes mellitus, and antibiotic therapy are the main causes of *vaginal candidiasis* [6]. The typical symptoms of *vaginal candidiasis* include pruritus, vaginal soreness, dyspareunia, external dysuria, and abnormal vaginal discharge [7]. Patients may be occasionally found to have *candida* based on a culture or Pap smear [8]. *Vulvovaginal candidias* is as an acute inflammatory disease, caused by *Candida* sp. especially *C. albicans* through non-*albicans* species of Candida (*C.glabrata, C.tropicalis* and *C.dubliniensis*) are also associated with recurrent diseases. *Candidiasis* is associated with intense pruritus, itching, dyspareunia, erythematous vulva, and cottage cheese like discharges, positive vaginal smear and culture, and a vaginal pH of less than 4.5. However, non-*albicans* species are usually less sensitive to azole antifungal agents [9,10]. Antifungal azole drugs provide the first treatments for *vaginal candidiasis*. Nevertheless, some side effects have been reported for this chemical medicine. Over-the-counter (OTC) of miconazole and clotrimazole medications for 7 days would provide a proper first-line therapy for women with occasional yeast vaginitis [11].

Several topical and oral antifungals such as clotrimazole is used for the treatment of *vaginal candidiasis* [12]. Nevertheless, some side effects, such as changes in hepatic enzymes, painful urination, depression, irritation, and dermatitis have been reported for clotrimazole [13]. Although it has no side effects during pregnancy, it is associated with embryotoxic effects. Thus, it should be consumed with caution during breast-feeding [14]. Also, the long-term use of antifungal drugs would lead to recurrent vaginitis [11]. Unavailability and high costs of the drugs in low-income societies, as well as their probable side effects and resistances have resulted in increased worries about synthetic chemicals [15]. In recent years, people have shown a growing interest in the general trends of natural remedies and herbal therapies when considering the lower costs, high availabilities, and lower side effects of plants and plant-based chemicals [16].

Since long time ago, plants have been used in traditional medicine practiced in almost all Asian countries including Iran. Herbal medicine still plays an essential role in various therapeutic fields, though synthetic applications of drugs in modern medicine have advanced over the past decades. In fact, the interest in herbal medications has been raised due to the therapeutic properties of plants. Several studies have revealed that plants have great amounts of natural antioxidants, as well as large anti-inflammatory [17], antibacterial [18], and antiviral [19] contents that make them highly important in the different aspects of medical applications. The fruit of *Quercus brantii* Lindl. is a source of tannins, catechins, gallic and ellagic acids, different galloyl and hexahydroxydiphenoyl derivatives, and oligomeric and polymeric proanthocyanidins [20]. Alcoholic Extract of Inner Stratum of *Q. Brantii* Fruit has antifungal effects on *Candida albicans* [21]. According to the literature, there are no reports on the effect of vaginal douche of Inner Stratum of *Q. Brantii* on *vaginal candidiasis*. Thus, the current investigation aimed at comparing the effects of two treatments, including vaginal douche of *Q. Brantii* extract and clotrimazole vaginal cream (1%) on *vaginal candidiasis* symptoms before and after the treatments in women.

2. Materials and Methods

2.1. *Patients*

This research was a randomized, case-controlled clinical trial. In this study, 89 non-pregnant women, who had a positive KOH test and culture of *vaginal candidiasis* and had been referred to the gynecology clinics of Shiraz University of Medical Sciences during 2016 were included into the study. To select the samples, convenience sampling were utilized and then we divided the patients into 2 groups based on the inclusion criteria of being married and having an age of 18-49 years and symptoms of *vaginal candidiasis*, respectively [22]. All the women were investigated for vaginal edema and erythema and other clinical symptoms of *vaginal candidiasis*. Also, only single sexual partners married to their respective spouses were chosen [3]. Other inclusion criteria were: having no abnormal vaginal or uterine bleeding, no known sensitivity to clotrimazole or other herbal drugs including *Q. Brantii* or known autoimmune diseases. Those women who were pregnant, had pelvic inflammatory diseases and lactation during the study, had menstruated during the study, and had taken hormone therapy, vaginal creams at least 7 days before the study, and anti-inflammatory, anti-fungal, and immunosuppressive drugs 14 days before the study were excluded from the research. All the patients signed an agreement form before participating in the investigation and after being informed about the study procedure [3]. The two codes of A and B, which respectively represented the treatments with clotrimazole vaginal cream (1%) and vaginal douche of *Q. Brantii*, were written on small pieces of paper and put into the relevant patients' pockets. The women were randomly divided into 2 experimental groups by permuted block randomization method. Group A (n=45) received clotrimazole vaginal cream (1%) and group B (n=44) received vaginal douche of *Q. Brantii*. The women in group A used a clotrimazole vaginal cream (1%) via a vaginal drug applicator for 7 nights, while those in group B dissolved the extract of *Q. Brantii* in 150 cc of distilled water to use vaginal douche of *Q. Brantii* for 7 nights. They were informed to lie on their backs for 30 minute after applying both the vaginal cream and douche.

2.2. Drugs and medications

Q. Brantii was collected from Kohgiluyeh and Boyer-Ahmad province, Iran, during 2015 and the inner stratum of the fruit was separated. The sample was authenticated and specified by with a voucher number at department of Phytopharmaceuticals, School of Pharmacy, Shiraz University of Medical Sciences. Clotrimazole vaginal cream 1% (Mycelex) was purchased, from Pars Daru Pharma-

ceutical Co., Tehran, Iran.

2.3. Extraction procedure

After collecting the fresh *Q. Brantii* fruit (100g), it was shade-dried at room temperature (25±2°C) far from the sunlight and grounded in the Pharmacology Laboratory of Shiraz University of Medical Sciences, Shiraz, Iran. Then, the obtained powder was statically extracted in 1000 ml of a hydroalcoholic solvent (70%) for 72 hours at 25±2°C. The yielded extract was filtered, concentrated and dried by vacuum evaporation. According to previous studies the extract's concentration was determined 5% [23], and the final extract with the concentration of 5% was dissolved in the water and was used as vaginal douche every night.

2.4. Study protocol

Those women referred to gynecology clinics of Shiraz University of Medical Sciences and having possible symptoms of *vaginal candidiasis* including: itching, vaginal discharge, dysuria, dyspareunia were selected for vaginal sampling. Before initiating the study and after taking the treatment procedures, a dry speculum was inserted into the vagina and the vaginal discharge from the posterior fornix were placed on a glass slide for performing the KOH test (evaluation of hyphae and mycelium by adding KOH 10%) and on a Sabouraud's dextrose agar plate for culture of *vaginal candidiasis* and counting the colonies, respectively. The patients were informed not to have sexual intercourse at least for 48 hours or clean their vaginas 72 hours before sampling. Sampling of all the patients was done during the follicular phase. The clinical symptoms, such as itching, vaginal discharge, dyspareunia, and dysuria reported by patients were compared before and after the treatments.

2.5. Laboratory analysis

The vaginal discharge samples were cultured in an incubator for yeast detection. By using a sterile cotton swap, the discharges were placed on the plates with media selective for Candidiasis growth (Sabouraud's dextrose agar). An additional sample of vaginal discharge was taken with another swap and rolled in a glass slide for determining the presence of hyphae and mycelium by adding KOH 10%. The results of the slides and cultures and colony counts were reported by an expert pathologist of Shiraz University of Medical Sciences.

2.6. Statistical analysis

The data of the samples were described, using descriptive statistics, which was presented as the mean ± SD for continuous and numbers (%) for categorical data. For analyzing both treatments, Independent t-test, and Chi-square test were used. $P<0.05$ was considered to indicate significant differences between the treatments. For data analysis, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. was used.

3. Results

All of the participants in both two groups completed the study. The demographic characteristics of the patients are presented in Table 1. According to the data, no significant differences were observed between the patients' distributions of the groups treated with clotrimazole vaginal cream and vaginal douche of *Q. Brantii* based on age, BMI, educational levels and contraceptive methods.

In both groups, most of the patients had used withdrawal or condoms, while the fewest of them had used IUD for contraception. The lowest educational levels of the patients were either an uneducated or high school level.

The results of the presence of patients' clinical symptoms of *vaginal candidiasis* are presented in Table 2. The prevalence of vaginal discharge was 90% in this study. No significant differences were discovered between the patients' vaginal discharge of the two groups before the treatments ($P>0.999$). However, vaginal discharge was significantly decreased in the group treated with vaginal douche of *Q. Brantii* compared to the group treated with clotrimazole vaginal cream after the treatment ($P=0.043$). Furthermore, no significant differences were observed between the groups regarding volvuvaginal itching as reported by patients, before ($P=0.55$) and after the treatments ($P=0.57$).

Also, no significant differences were seen between the groups in terms of dysuria ($P>0.999$), dyspareunia ($P=0.823$) and vaginal edema and erythema ($P>0.999$) after the treatments.

Based on the evidence of the patients' cultures of vaginal discharge (Table 3), no significant differences were seen between the groups considering the positive and negative culture growth, before and after the treatments ($P=0.251$).

As can be observed in Table 4, there were no significant differences between the colony counts of the patients' cultures in the two groups of clotrimazole vaginal cream and vaginal douche of before ($P=0.188$) and after the treatments ($P=0.850$).

4. Discussion

Infection of the lower genital tract is one of the principal reasons for providing gynecological care for women [24]. Due to the importance and association of vaginitis with Sexually Transmitted Diseases (STDs), several researches have been done with better and more comprehensive options of treatment [25]. The availability of a wide spectrum of therapeutic options has led to the discovery of the principal causes of vaginitis [26]. Despite the fact that chemical drugs are widely utilized for the treatment of infections, side effects, resistance, and high economic costs are the main limiting factors of these drugs [27]. Considering the problems of side effects and drug resistance, there is a current growing interest in complementary and alternative medicine (CAM) in general [28]. In this regard, Ebrahimi et al. [29] studied the antimicrobial effects of various agents of oak fruit extract against *Escherichia coli* bacteria and reported that the extract has acceptable antimicrobial

Table 1 The demographic characteristics of participants

Characteristics	Clotrimazole vaginal cream (n = 40)	Vaginal douche of *Q. Brantii* (n = 40)	P-value
Age (Mean±SD)	33.65±8.28	35.70±8.28	0.403
BMI (Mean±SD)	23.65±4.90	23.45±4.20	0.911
Educational level (%)			0.862
Un-educated	5 (12.5)	7 (17.5)	
Primary	9 (22.5)	5 (12.5)	
Secondary	7 (17.5)	7 (17.5)	
High school	4 (10)	3 (7.5)	
Diploma	8 (20)	10 (25)	
Academic	7 (17.5)	8 (20)	
Contraceptive methods (%)			0.702
Ocp	5 (12.5)	5 (12.5)	
Condom	9 (22.5)	7 (17.5)	
IUD	4 (10)	3 (7.5)	
Injections	4 (10)	6 (15)	
Tubectomy	3 (7.5)	7 (17.5)	
Withdrawal	12 (30)	11 (27.5)	
Other	3 (7.5)	1 (2.5)	

Table 2 The patients' clinical symptoms of both groups before and after the treatment, N (%)

Variables	Clotrimazole vaginal cream (n = 40)	Vaginal douche of *Q. Brantii* (n = 40)	P-value
Vaginal discharge			
Before	36 (90)	36 (90)	>0.999
after	8 (20)	2 (5)	0.043
volvuvaginal itching			
Before	24 (60)	28 (70)	0.552
after	7 (17.5)	9 (22.5)	0.570
dysuria			
Before	23 (57.5)	23 (57.5)	>0.999
after	11 (27.5)	13 (32.5)	>0.999
Dysparounia			
Before	19 (47.5)	18 (45)	0.823
After	10 (25)	11 (27.5)	0.823
Edema and erythma			
Before	23 (57.5)	23 (57.5)	>0.999
After	0 (0)	0 (0)	-

Table 3 The evidence of the patients' cultures of vaginal discharge between the groups before and after the treatment, N (%)

	Clotrimazole vaginal cream (n=40)	Vaginal douche of *Q. Brantii* (n=40)	P-value
Culture growth	**Before the treatments**		
positive	40 (100)	40 (100)	
negative	0 (0)	0 (0)	-
	After the treatments		
positive	5 (12.5)	10 (25)	0.251
negative	35 (87.5)	30 (75)	

Table 4 The colony counts of patients' cultures in both groups, N (%)

	Clotrimazole vaginal cream	Vaginal douche of *Q. Brantii*	P-value
Colony counts	**Before the treatments**		
0-100	2 (5)	0 (0)	
101-200	12 (30)	8 (20)	0.188
201-300	26 (65)	32 (80)	
	After the treatments		
0-100	35 (87.5)	30 (75)	0.850
101-200	4 (10)	9 (22.5)	
201-300	1 (2.5)	1 (2.5)	

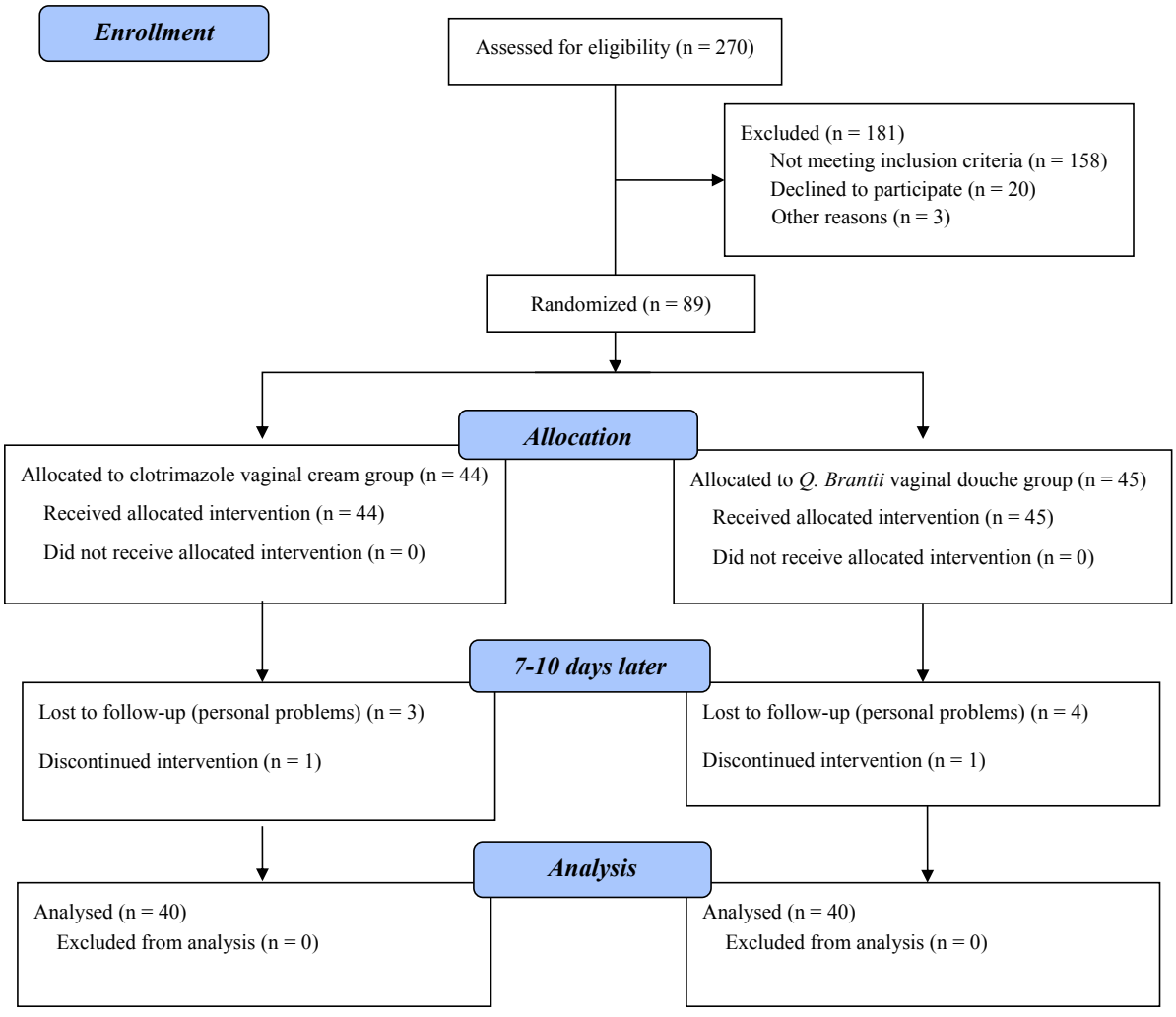

Figure 1 Flow diagram showing patients' recruitment and procedures (CONSORT 2010)

activities. Also, the alcoholic extract of *Q. Brantii* fruit has antimicrobial activities on *Staphylococcus aureus*, *Staphylococcus* epidermidis, and *Escherichia coli* [30].

In this research, *vaginal candidiasis* was significantly reduced in the regard of *Candidiasis* culture in *Q. Brantii*-treated group as compared to the group receiving clotrimazole vaginal cream. Improvements in clinical symptoms were not different among the groups. Khosravi et al. [31] investigated the therapeutic effects of Zataria multiflora cream and clotrimazole cream on acute *vaginal candidiasis*. They reported Zataria multiflora cream (0.1%) to alleviate erythema and satellite vulvar lesions, vulvar and vaginal edemas and *vulvovaginal* excoriations in patients [31].

Antibacterial activities are involved in a complex mechanism like inhibitions of cell wall metabolism and synthesis, as well as cell memberane, nucleic acid, and protein [31]. Since having phenolic components, *Q. Brantii* fruit appears to induce a toxic effect against pathogens by reacting with sulfhydryl groups or more nonspecifically interacting with proteins through oxidized compounds [32]. Also, it is probable that the levels of phenolic compounds in *Q. Brantii* fruit enhance in response to pathogen infection [33]. Furthermore, linalool, geraniol, and terpinen-4-ol compounds as the representatives of oxygenated monoterpenes have been found to show the strongest antifungal activities against *Candida albicans* by deforming its cell wall membrane [34]. This pathogen impresses its effect by binding to host cells and inducing morphological changes in them through proteinase and phospholipase secretions [35]. Nonetheless, merit studies are required to clarify the pharmacological properties and mechanisms of phenolic compounds in *Q. Brantii* fruit extract. It has been reported that terpenes, phenols, carvacrol, flavonoids, eugenol, thymonin, and rosmarinic acids reduce the virulence properties of *Candida albicans* [36]. Moreover, furocoumarins, which are available in *Q. Brantii*, inhibit the growth of bacteria by interacting with the bacterial DNA [37,38].Overall, terpenes and flavonoids (natural phenols) constitute the active antifungal compounds of essential oils. It seems that their antifungal or antibacterial mechanisms are related to those of other compounds [39]. Moreover, the antimicrobial activities of essential oils are dependent on their main components and synergistic or antagonistic effects [40].

5.Conclusion

In conclusion, the new findings of this study revealed that the bioactive substances existing in the inner stratum of *Q. Brantii* fruit have anti-fungal activities against *vaginal candidiasis*. The results of this research suggested almost similar therapeutic effects of the vaginal douche of Inner Stratum of *Q. Brantii* and clotrimazole vaginal cream. However, considering the limitation of the study such as unknown sensitivity to the new treatment, more studies are needed to determine the vaginal douche effect of *Q. Brantii* in clinical trials.

Acknowledgment

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Conflict of interest

The authors declare that there are no conflicts of interest.

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