



OPEN

Comparing the effects of Mycozin and Clotrimazole 1% creams on vaginal candidiasis: a triple-blinded randomized controlled trial

Khadije Hajizadeh¹, Zahra Alivand¹, Vahideh Rahmani², Leila Mehrannia³, Sanam Nami⁴, Behrooz Shokouhi⁵ & Mojgan Mirghafourvand⁶✉

Clotrimazole 1% and Mycozin vaginal cream have been reported to be effective in relieving the symptoms of vulvovaginitis caused by *Candida*. The resistance to azole compounds, and the side effects of chemical drugs have been reported following azole therapy. It was hypothesized that Mycozin is at least as effective as Clotrimazole in treating vaginal candidiasis. This equivalent, triple-blinded, randomized clinical trial was conducted on 126 patients who complained of vaginal itching referred to Al-Zahra Teaching Hospital, Tabriz, Iran between September 2023 and May 2024. Participants were divided into two groups, i.e., Mycozin (n = 64) and Clotrimazole 1% (n = 62), using the block randomization method. The patient's complaints, clinical signs, the pH and culture of the secretions was recorded before and after treatment. The patient's improvement, level of satisfaction, and side effects were recorded. The data were analyzed using Pearson chi-square test, ANCOVA, and Mann–Whitney U test. There was no statistically significant difference between the two groups regarding the mean pH (Adjusted mean difference: 0.01; 95% Confidence Interval (CI): -0.20 to 0.21, P = 0.965), and microscopic evaluation (Odds Ratio (OR): 0.61; 95% CI: 0.28 to 1.36, P = 0.230). After the treatment the frequency of itching in the Clotrimazole group (N = 13; 22.0%) was lower than that of the Mycozin group (N = 26; 43.3%) (OR: 0.37; 95% CI: 0.17 to 0.82; P = 0.013). There was no statistically significant difference in other symptoms and signs before and after the treatment (P > 0.05). Also, there was no statistically significant difference between the two groups in the level of satisfaction (P = 0.056) and patient improvement (P = 0.074). The side effects of treatment with Mycozin and Clotrimazole were observed in eleven and five patients, respectively. Considering the efficacy of Mycozin vaginal cream in eliminating most of the symptoms and signs associated with vaginal candidiasis and its positive effect in negating the results of culture, it can be used as a suitable alternative in the treatment of vaginal candidiasis in patients interested in herbal medicines and resistant to azole compounds.

Trial registration: Iranian Registry of Clinical Trials (IRCT): IRCT20120718010324N77. Date of registration: 20/05/2023; URL: <https://irct.behdasht.gov.ir/user/trial/68718/view>; Date of first registration: 31/05/2023.

Keywords Mycozin, Clotrimazole, Vaginal candidiasis

Abbreviations

| | |
|--------|-------------------------------------|
| ANCOVA | Analysis of covariance |
| IRCT | Iranian Registry of Clinical Trials |
| SDA | Sabouraud dextrose agar |

¹Midwifery Department, Faculty of Nursing and Midwifery, Tabriz University of Medical Sciences, Tabriz, Iran. ²Women Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. ³Medical Biotechnology Department, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran. ⁴Parasitology and Mycology Department, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. ⁵Pathology Department, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. ⁶Social Determinants of Health Research Center, Faculty of Nursing and Midwifery, Tabriz University of Medical Sciences, Tabriz, Iran. ✉email: mirghafourvandm@tbzmed.ac.ir

| | |
|-----|---------------------|
| ITT | Intention-to-treat |
| SD | Standard deviation |
| CI | Confidence interval |

As far as infections of the female genital tract are concerned, vaginitis is the most common and one of the most frequent reasons why women visit a clinic¹. They account for about 80% of non-routine visits in non-pregnant individuals^{1,2}. *Candida albicans*, *Trichomonas vaginalis*, and *Gardnerella vaginalis* are the three most common factors causing vaginitis^{3,4}, and infection with *Candida albicans* is the second most common cause of vaginitis¹. On average, 75% of women suffer from vulvovaginal candidiasis at least once in their lifetime^{5,6}. In Iran, in one study the prevalence of vaginitis was reported to be 41.3%. Of the three infectious agents mentioned, *Candida* was the most common pathogen with an incidence of 47.4%⁷. Predisposing factors for this type of vaginitis include uncontrolled diabetes, obesity, use of birth control pills and antibiotics, use of intrauterine devices for contraception, pregnancy, and a weak immune system^{1,8–10}.

Vulvovaginal candidiasis is accompanied by cheesy secretions, inflammation and redness, severe itching, and sometimes ulcers or abscesses, and in severe cases, it also affects the perineum and the inner parts of the groin area. It can even cause dysuria or dyspareunia^{1,11–13}. All these complications can affect the quality of life of those affected, especially their sexual life. As sexual relationships play an important role in mental health, the treatment of vaginal candidiasis is of particular importance¹⁴. Various studies have used different drugs such as nystatin, antifungal agents with azole compounds such as Clotrimazole, Miconazole, Ketoconazole, and herbal remedies such as Mycozin, *Zataria multiflora*, etc.^{1,15,16}.

Clotrimazole 1% vaginal cream is one of the most effective drugs in the treatment of vaginal candidiasis. However, like most chemical medications, it has side effects such as burning, itching, redness, and skin dryness¹⁷. In addition to treatment with chemical antifungals, the possibility of developing microbial resistance due to their repeated use is high. *Candida* species are especially concerning because they are a leading cause of systemic fungal infections with mortality rates reaching 50%. Most *Candida* infections are caused by *Candida albicans* and in a study 49.2–100% of isolates of this species that collected from vaginal swab samples are reportedly resistant to some azoles^{18,19}. Also, in taking medication, patients may complain of side effects such as changes in the taste in the mouth, nausea, and diarrhea¹⁷.

Garlic, scientifically known as "*allium sativum*", from the tulip family (Liliaceae), has long been used in the treatment of infections^{20,21}. It is a powerful antifungal herb with antimicrobial properties²². Thyme, from the mint family, also is another herb known to treat bacterial and fungal infections²³. Meanwhile, Mycozin vaginal cream has been reported to be effective in relieving the symptoms of vulvovaginitis caused by *Candida*¹⁵. The ingredients of this cream are garlic and thyme. Thyme extract was added to the cream to neutralize the smell of garlic. It has an antifungal effect and synergistically enhances the therapeutic effect of garlic²⁴.

In a single blind study with 64 participants, the results showed that a vaginal cream containing garlic and thyme was as effective as a Clotrimazole vaginal cream in the treatment of vaginal candidiasis, and there was no difference in the responses to treatment with these two drugs²⁵. Farshbaf-Khalili et al.¹⁶ showed that the effect of the three vaginal creams of garlic, *Zataria multiflora* and Clotrimazol was the same in the treatment of vaginal candidiasis, prevention of recurrence and improvement of clinical symptoms and signs. Khosravi et al²⁶ reported that the use of thyme vaginal cream was effective in reducing discharge and itching caused by vulvovaginal candidiasis.

The use of medicinal herbs is the oldest human approach to treat disease and it is used in many parts of the world, especially in regions with limited access to chemical medicines²⁷. Considering the microbial resistance to azole compounds, especially Clotrimazole, the side effects of chemical drugs, the high prevalence of vaginal candidiasis, the tendency of people to use herbal medicines, the present study was conducted to compare the effects of Mycozin vaginal cream and 1% Clotrimazole vaginal cream in treating vaginal candidiasis. This decision is further supported by a previous study²⁵ that compared the two therapies; however, that study had limitations, including a single-blind design and a smaller sample size.

Study hypothesis

- Mycozin vaginal cream is as effective as Clotrimazol 1% vaginal cream in eliminating laboratory-confirmed cases of vaginal candidiasis.
- Mycozin vaginal cream is as effective as Clotrimazol 1% vaginal cream in eliminating symptoms of vaginal candidiasis.
- Mycozin vaginal cream is as effective as Clotrimazol 1% vaginal cream in eliminating signs of vaginal candidiasis.
- The mean pH of vaginal secretions is similar in both groups.
- The treatment satisfaction is similar in both groups.

Methods

Study design and participants

This study is the result of a project approved by the Vice Chancellor for Research of Tabriz University of Medical Sciences under the ethical code (IR.TBZMED.REC.1402.112) and registration code (IRCT20120718010324N77) on the Iranian Registry of Clinical Trials website. This equivalent, triple-blinded, randomized clinical trial was conducted on 126 patients referred to Al-Zahra Teaching Hospital, Tabriz, Iran between September 2023 and May 2024.

The inclusion criteria were as follows: married women aged 18–45 years who had symptoms of vaginal candidiasis and were literate. The exclusion criteria were as follows: Suffering from chronic diseases such as

diabetes, acquired immune deficiency syndrome (AIDS), immune system disorders, depression, use of antibiotics and corticosteroids in the last two weeks, the presence of severe psychological distress in the last three months, such as the death of a first-degree relative. The other exclusion criteria were as follows: menstruation at the time of the study, use of oral contraceptives, presence of a sore or lump in the cervix when viewed with a speculum, the presence of a known pregnancy or breastfeeding at the time of the study, the use of other medications to treat vaginitis, recurrent vulvovaginitis (more than four times per year), abnormal uterine bleeding, allergy to herbal medicines and allergy to azole-containing agents.

Based on the study by Saffari et al.²⁸ regarding the incidence of negative cultures after treatment and using G-Power software, considering $P_1=0.77$, $P_2=0.52$ (assuming a non-inferiority margin of 25%, two-sided $\alpha=0.05$), and power = 80%, the sample size was calculated to be 57 individuals in each group. With considering 10% attrition, the final sample size was 63 in each group.

Sampling

The convenience sampling method was used in this study. The researcher attended in Al-Zahra Teaching Hospital, Tabriz, Iran and after introducing and explaining the objectives of the study, obtained written informed consent from those who complained of vulvovaginal itching and discharge and were willing to participate in the study; A questionnaire on demographic characteristics and history of illness and complaints was completed.

The participants were examined in full compliance with ethical principles. After vaginal examination and direct observation with the speculum without the use of lubricant, clinical signs were checked and the pH of the secretions was recorded with a paper pH meter in the clinical observation checklist.

To diagnose vulvovaginal candidiasis, a sterile swab was taken from the posterior fornix of the vagina of the symptomatic women. The sample was placed in a tube containing sterile physiologic serum and cultured in Sabouraud Dextrose Agar (SDA; Merck, Germany) containing 0.05% chloramphenicol (Sigma Aldrich, USA) and incubated at 37 °C for 24–48 h; colonies were then streaked onto a slide and assessed microscopically after adding 1–2 drops of 10% potassium hydroxide (KOH 10%) to the slides. Light microscopy with magnification of 40× was utilized for observing candida hyphae and, in the case of growth of the fungus in the dextrose agar plate, the culture was considered positive.

In the case of a definitive diagnosis of vaginal candidiasis based on the secretion culture and the presence of yeasts on microscopic examination, participants were invited to visit the selected center to start treatment if they wished and were informed of the confidentiality of their information and the possibility of leaving the study at any time.

Randomization

Participants were divided into two groups, i.e., Mycozin (N = 64) and Clotrimazole 1% (N = 62), using the block randomization method, using Random Allocation Software (RAS) with a block size of 4 and 6. The researcher, all participants and outcome assessor were blinded.

Mycozin and Clotrimazole creams, in similar packaging, were labeled and numbered from 1 to 126 according to the allocation order by a person not involved in the sampling and data collection. After random and concealed allocation, the drugs were administered to each participant in the order of their participation in the study.

Both creams were produced by the Goldaru Pharmaceutical Company in Isfahan and were similar in shape, color, and size. In addition to the medication, the participants received seven applicators, an information booklet on how to take the medicine, dietary and health recommendations, abstaining from sexual intercourse during treatment or using a condom during intercourse, and a form to document the use of the medication after each application. They were also told how to take the medication in the form of an applicator equivalent to five grams for a week at bedtime and to come back for a follow-up 10–15 days after starting the treatment. They were also asked to pay attention to hygiene during the treatment period and not to use vaginal douches, vaginal creams, and other medications for vaginal candidiasis.

Follow up

During the follow-up examinations, the patient's complaints were asked again and recorded in the checklist. In addition, the patient was examined, the clinical signs were recorded, the pH of the secretions was measured, a sample of the vaginal secretions was taken for culture, and the results were recorded on the appropriate forms. The patient's improvement, level of satisfaction, and side effects were recorded. All untreated patients were treated with the routine treatment (Clotrimazole 1%).

Data collection tools

Socio-demographic characteristics form

This form, which was completed by participants before treatment, included the variables of age, education, work status, husband's education and occupation, last birth method, contraceptive use, date of current contraceptive use, gravida, para, medical history, medication history, and age at first marriage.

Clinical observations checklist

This checklist, completed by the researcher before and after the treatment, included items about the cervix's appearance, vulvovaginal erythema, amount, consistency, color, odor, and appearance of discharge. The vaginal discharge pH and culture were also evaluated.

Patient complaints checklist

This checklist completed by the participants before and after the treatment included items about vaginal odor, dysuria, urinary frequency, itching, itching in intercourse, lower abdominal pain, irritation in intercourse, and dyspareunia.

Content and face validity were used to determine the validity of the socio-demographic characteristics form, clinical observations checklist, and patient complaints checklist.

Data analysis

The collected data was analyzed using SPSS 21 software and the Kolmogorov–Smirnov test was used to assess the normality of the data. The Independent t, Pearson chi-square and Fisher exact tests were used to compare socio-demographic and obstetric characteristics between groups. The Pearson chi-square test was used to compare clinical observations, patient complaints, and microscopic evaluation before and after treatment. The chi-square test is a non-parametric (distribution-free) test used to analyze group differences when the dependent variable is measured at the nominal level²⁹. An ANCOVA was also performed to compare vaginal pH after treatment with adjusting of baseline value. ANCOVA is a powerful statistical method that analyzes the differences between groups means while controlling for the effects of at least one continuous covariate to account for baseline differences³⁰. The Mann–Whitney U test was used to compare level of satisfaction and patient improvement after treatment because the variables are single ordinal with no specific distribution³¹. The intention-to-treat (ITT) method was used for data analysis. The p-value < 0.05 was considered significant.

Results

The present study was performed on 126 patients referred to Al-Zahra Teaching Hospital from September 2023 to May 2024. A total of 166 women were examined, of whom 40 were excluded due to not meeting the inclusion criteria or their unwillingness to participate. Finally, 126 individuals participated in the study and were randomly assigned to Mycozin and Clotrimazole 1% groups. Four participants in the former group and three in the latter group were reluctant to continue the study (Fig. 1).

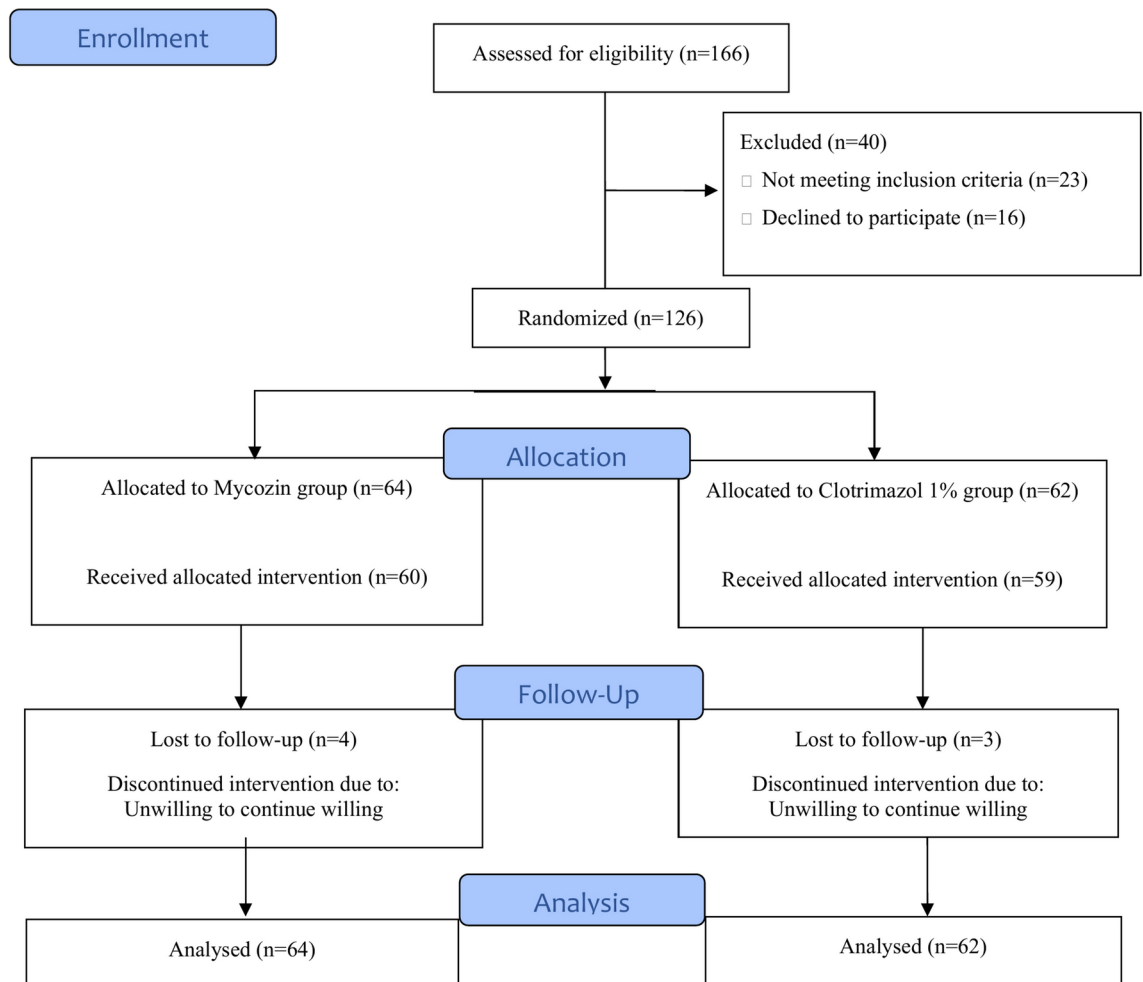


Fig. 1. Flow chart of the study.

The mean (SD) age in these two groups was 39.23 (6.59) and 39.21 (6.56) years, respectively. Most of the participants had a diploma, were housewives, and applied fertility awareness methods to prevent pregnancy. This study did not show a statistically significant difference between the two groups regarding socio-demographic characteristics (Table 1).

The mean (SD) pH before the intervention in the Mycozin and Clotrimazole 1% groups was 4.77 (0.77) and 4.81 (0.84), respectively. 10–15 days after the treatment, the mean (SD) pH in these groups was 4.92 (0.88) and 4.95 (0.83); respectively (Fig. 2). There was no statistically significant difference between the two groups regarding the mean pH after treatment based on the ANCOVA test with adjusting the baseline value (Adjusted mean difference:AMD: 0.01; 95% Confidence Interval (CI): -0.20 to 0.21, $P=0.965$) (Table 2).

The frequency of negative culture, 10–15 days after the treatment, was 39 (65.0%) in the Mycozin group and 44 (74.5%) in the Clotrimazole 1% group. There was no statistically significant difference between the treatment groups regarding microscopic evaluation (Odds Ratio (OR): 0.61; 95% CI: 0.28 to 1.36, $P=0.230$) (Table 2).

After the treatment the frequency of itching in the Clotrimazole group ($N=13$; 22.0%) was lower than that of the Mycozin group ($N=26$; 43.3%) (OR: 0.37; 95% CI: 0.17 to 0.82; $P=0.013$). There was no statistically significant difference in other complaints and symptoms such as vaginal odor, dysuria, urinary frequency, itching and irritation in intercourse, dyspareunia, and lower abdominal pain between the two groups before and after the treatment ($P>0.05$) (Table 3).

In the vaginal examination, there was no statistically significant difference considering cervical appearance, vulvovaginal erythema, amount, consistency, color, and appearance of discharge between the groups before the treatment ($P>0.05$). Also, there was no statistically significant difference in the signs in the follow-up between the two groups ($P>0.05$) (Table 3).

There was no statistically significant difference between the two groups in the level of satisfaction ($P=0.056$) and patient improvement ($P=0.074$) 10–15 days after the treatment (Table 4).

The side effects of treatment with Mycozin were observed in 11 patients by symptoms of intensification of itching ($N=4$; 6.3%), intensification of irritation ($N=3$; 4.7%), skin redness ($N=3$; 4.7%), skin dryness ($N=1$; 1.6%). In addition, the side effects of treatment with Clotrimazole 1% were observed in five patients with the intensification of itching ($N=1$; 1.6%), intensification of irritation ($N=3$; 4.8%), and skin redness ($N=1$; 1.6%) (Table 5).

Discussion

The results of the study showed that Mycozin vaginal cream was as effective as Clotrimazole 1% vaginal cream in eliminating most of the symptoms, signs and laboratory results.

In the present study, there was no statistically significant difference between the two groups concerning the mean pH value of the vaginal secretions after treatment. In a review of the literature, no study examined the pH of vaginal secretions after treatment with garlic- or Clotrimazole-containing medications. In vaginal candidiasis, the vaginal pH is normal and ranges from 4–4.5³². In this study, the pH of vaginal secretions before treatment was in the range of 4–5, which remained constant after treatment. Given the normal pH of the vagina in candidiasis, this pH range is to be expected.

In this study, based on the culture results in SDA, patient recovery in the Mycozin group was similar to Clotrimazole 1% vaginal cream. In line with the results of the present study, Farshbaf-Khalili et al.¹⁶ found no significant difference between the recovery of patients with vaginal candidiasis based on the results of culturing in agar in three groups receiving vaginal cream with garlic, *Zataria multiflora* and Clotrimazole 2%, seven and 30 days after treatment. In the study by Alizadeh et al.¹⁵, the improvement of patients was similar in the Mycozin group as in the vaginal Miconazole group, based on the results of cultivation and smear. In contrast to the present study, the results of the study by Watson et al.³³ in asymptomatic women whose vaginal secretions were positive for *Candida* showed no effect of oral ingestion of three garlic tablets twice daily for two weeks before menstruation compared to the placebo group immediately after treatment on vaginal *Candida* colonization.

Before treatment, 68.8% of patients in the Mycozin group and 80.6% in the Clotrimazole group complained of itching. In agreement with the results of the present study, Farshbaf-Khalili et al.¹⁶ showed that genital itching was the most common symptom experienced by patients before treatment. In our study, Clotrimazole 1% vaginal cream had a significantly better effect in eliminating itching than Mycozin, which could be because more side effects (intensification of itching) occurred in the Mycozin group than in the Clotrimazole 1% group. Contact dermatitis due to plants applied topically for medical purposes has often been described. Case reports have mentioned the possibility that garlic or thyme may cause allergic reactions (allergic contact dermatitis, irritation and itching)^{34,35}. In contrast to the results of this study, Farshbaf-Khalili et al.¹⁶ found no significant difference between the improvement of pruritus seven and 30 days after treatment in three groups receiving vaginal cream with garlic, *Zataria multiflora*, and Clotrimazole 2%. In the present study, both creams were similar in eliminating other symptoms and complaints of the patients except for itching. In line with the results of this study, Farshbaf-Khalili et al.¹⁶ showed no significant difference before, seven, and 30 days after treatment between the three groups receiving vaginal cream with garlic, *Zataria multiflora*, and Clotrimazole 2% in terms of decrease in patients' complaints such as cheesy discharge, urine irritation, irritation and pain during intercourse. In the study by Alizadeh et al.¹⁵ itching was the most common symptom experienced by patients before treatment, and the disappearance of all symptoms (vaginal odor, dysuria, urinary frequency, itching, itching and irritation during intercourse, and dyspareunia) in the Mycozin group was similar to that in the vaginal Miconazole group. In contrast to the present study, the study by Watson et al.³³ in women whose vaginal secretion culture was positive for *Candida* showed a statistically significant difference in patient-reported symptoms such as moderate and severe vaginal itching and the presence of vaginal discharge in both groups receiving three oral garlic tablets twice daily and a placebo two weeks before treatment. Using different dosage forms with longer treatment

duration (two weeks), the small sample size, the immediate post-treatment follow-up, and the comparison of the herbal medicine group with the placebo group in their study may justify this difference.

In this study, the disappearance of clinical observations in the Mycozin group was similar to Clotrimazole 1% vaginal cream. These results are consistent with those of Farshbaf-Khalili et al.¹⁶, in which there was no significant difference in the relief of clinical symptoms of vulvovaginal erythema, abnormal cervical appearance, abnormal discharge, non-homogenous discharge, non-transparent discharge, cheesy discharge and vaginal inflammation between the groups receiving vaginal cream with garlic, *Zataria multiflora* and Clotrimazole 2% at seven and 30 days after treatment. Alizadeh et al.¹⁵ showed that seven days after treatment, the effect of Mycozin and Miconazole vaginal creams was the same in eliminating the clinical symptoms of inflammation, consistency, color, odor, quantity, and appearance of vaginal discharge. Fouladi et al.³⁶ showed that both vaginal preparations containing thyme and Clotrimazole were effective in improving clinical symptoms such as discharge, itching, irritation, and dyspareunia.

By penetrating the membrane of *Candida* cells and organelles such as mitochondria, garlic can eventually lead to membrane destruction and cell death³⁷. In addition to the direct effect on the fungus demonstrated in vitro, thyme extract has immunosuppressive effects and can thus destroy the fungus³⁸. The mixture of garlic and thyme with its synergistic effect can be effective in *Candida* treatment³⁹.

This study showed that treatment satisfaction and patient improvement were the same in the Mycozin and Clotrimazole 1% groups. In addition, the results showed that side effects occurred in both groups. The most common side effect of the Mycozin group was intensification of itching and that of the Clotrimazole group was intensification of irritation. The least common side effect in both groups was skin dryness. Bahadoran et al.²⁵ showed that the most common side effect in the groups receiving vaginal cream with garlic and thyme and Clotrimazole vaginal cream was related to itching and the least common side effect in both groups was vaginal dryness. In the study by Watson et al.³⁰, side effects were significantly higher in the group of women with vaginal candidiasis who received oral tablets with garlic than in the placebo group. These side effects included gastrointestinal symptoms, i.e., stomach pain, garlic odor, and nausea, which may be due to oral ingestion of the drug.

The strengths of the present study were the large sample size, random allocation with allocation concealment to prevent selection bias, blinding of both participants and outcome assessor to mitigate performance and detection bias. Additionally, the use of an herbal vaginal cream containing garlic, complemented by thyme to neutralize the garlic odor and enhance its efficacy, contributed to the treatment of vaginal candidiasis. One of the weaknesses of this study was the short follow-up period to check the recurrence of vaginitis signs and symptoms. In this study, the women with chronic diseases such as diabetes, AIDS, depression, immune system disorders were excluded; so, the results cannot be generalized to women with mentioned chronic diseases. It is recommended that similar studies be conducted examining *Candida* species and symptom recurrence in long term follow up in women with recurrent vaginal candidiasis.

Conclusion

The results of this study show that both creams, Mycozin and Clotrimazole 1%, were effective in the treatment of vaginal candidiasis. Given the efficacy of Mycozin vaginal cream in alleviating symptoms and signs of vaginal candidiasis, its ability to yield negative results in vaginal secretion cultures, and its economical nature without serious side effects, it presents a suitable alternative or complementary therapy for treating vaginal candidiasis. This is especially relevant for patients interested in herbal remedies and those resistant to azole compounds.

| Variables | Mycozin N = 64 | Clotrimazole N = 62 | P |
|--|------------------------|------------------------|--------------------|
| | Mean (SD) ^a | Mean (SD) ^a | |
| Age (years) | 39.23 (6.59) | 39.21 (6.56) | 0.983 ^b |
| Age at first marriage (years) | 20.95 (5.06) | 19.73 (4.53) | 0.154 ^b |
| Time of current contraceptive use (months) | 83.73 (59.68) | 70.37 (58.10) | 0.205 ^b |
| | (N %) | (N %) | |
| Education level | | | 0.421 ^c |
| Elementary | 14 (21.9) | 12 (19.4) | |
| Intermediate | 7 (10.9) | 9 (14.5) | |
| High school | 3 (4.7) | 5 (8.1) | |
| Diploma | 19 (29.7) | 27 (43.5) | |
| University | 21 (32.8) | 9 (14.5) | |
| Work status | | | 0.916 ^d |
| House keeper | 48 (75.0) | 47 (75.8) | |
| Employed | 16 (25.0) | 15 (24.2) | |
| Husband's education | | | 0.833 ^c |
| Illiterate | 5 (7.8) | 2 (3.2) | |
| Elementary | 3 (4.7) | 10 (16.1) | |
| Intermediate | 15 (23.4) | 10 (16.1) | |
| High school | 5 (7.8) | 6 (9.7) | |
| Diploma | 21 (32.8) | 21 (33.9) | |
| University | 15 (23.4) | 13 (21.0) | |
| Husband's job | | | 0.893 ^e |
| Unemployed | 1 (1.6) | 1 (1.6) | |
| Worker | 6 (9.4) | 7 (11.3) | |
| Employed | 16 (25.0) | 12 (19.4) | |
| Self-employed | 41 (64.1) | 42 (67.7) | |
| Last birth method | | | 0.353 ^d |
| Non | 11 (17.2) | 8 (12.9) | |
| Natural vaginal delivery | 20 (31.3) | 27 (43.5) | |
| Cesarean section | 33 (51.6) | 27 (43.5) | |
| Contraception method | | | 0.255 ^e |
| Barrier methods | 8 (12.5) | 6 (9.7) | |
| Intra uterine device | 2 (3.1) | 8 (12.9) | |
| Fertility awareness methods | 33 (51.6) | 28 (45.2) | |
| Tubal ligation | 7 (10.9) | 3 (4.8) | |
| Vasectomy | 2 (3.1) | 1 (1.6) | |
| Injections | 0 (0.0) | 1 (1.6) | |
| Non | 12 (18.8) | 15 (24.2) | |
| Gravida | | | 0.536 ^d |
| 0 | 11 (17.2) | 7 (11.3) | |
| 1-2 | 23 (35.9) | 27 (43.5) | |
| ≥ 3 | 30 (46.9) | 28 (45.2) | |
| Continued | | | |

| Variables | Mycozin N = 64 | Clotrimazole N = 62 | P |
|-----------------|------------------------|------------------------|--------------------|
| | Mean (SD) ^a | Mean (SD) ^a | |
| Para | | | 0.360 ^d |
| 0 | 11 (17.2) | 8 (12.9) | |
| 1-2 | 42 (65.6) | 37 (59.7) | |
| ≥3 | 11 (17.2) | 17 (27.4) | |
| Medical history | 9 (14.1) | 15 (24.2) | 0.148 ^d |
| Drug history | 8 (12.5) | 6 (9.7) | 0.614 ^d |

Table 1. Socio-demographic characteristics between groups (n = 126). ^aStandard deviation, ^bindependent samples T, ^cChi-square for trend, ^dPearson Chi-square, ^eFisher's exact test.

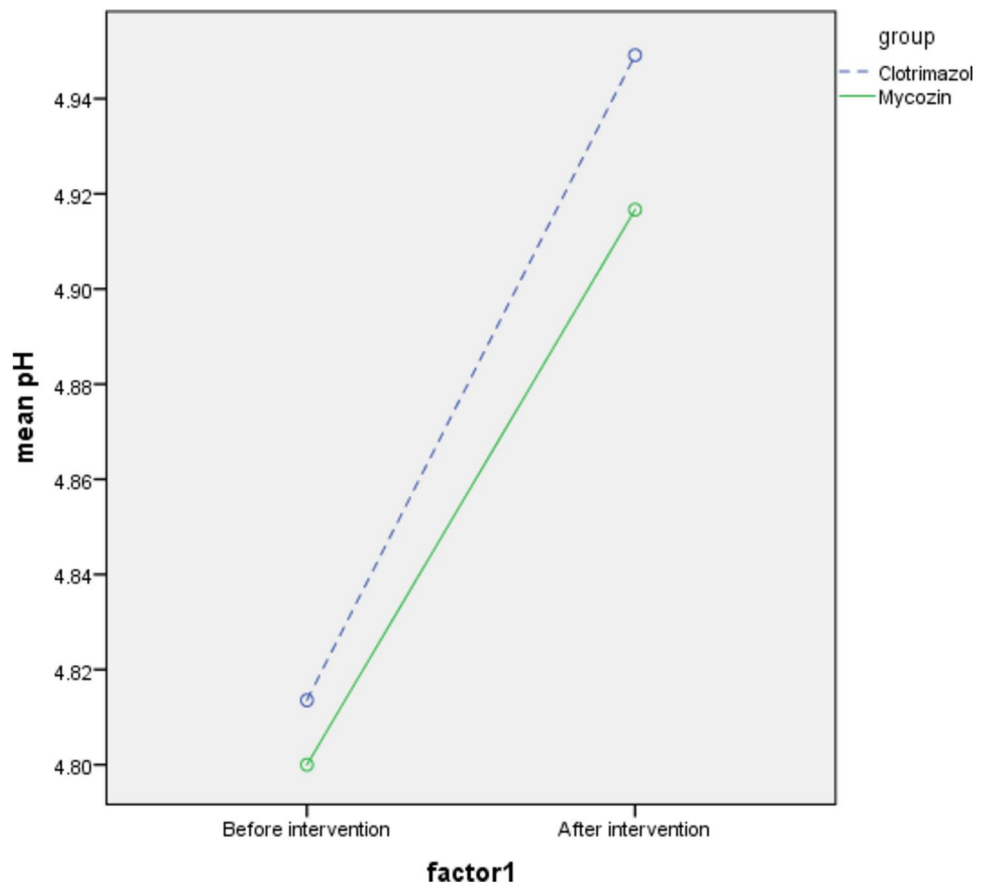


Fig. 2. Comparison of the vaginal pH between groups before and after treatment.

| Variables | Mycozin (n = 64) | Clotrimazole (n = 62) | Effect size (95% CI) ^b | P |
|-------------------------------|------------------------------|------------------------------|---|--------------------|
| Vaginal pH^a | Mean (SD)^a | Mean (SD)^a | Mean difference (95% CI)^b | |
| Before treatment | 4.77 (0.77) | 4.81 (0.84) | 0.04 (-0.24 to 0.33) | 0.778 ^c |
| After treatment | 4.92 (0.88) | 4.95 (0.83) | 0.01 (-0.20 to 0.21) | 0.965 ^d |
| Positive culture | N (%) | N (%) | Odds ratio (95% CI)^b | |
| Before treatment | 64 (100.0) | 62 (100.0) | | |
| After treatment | 21 (35.0) | 15 (25.4) | 0.61 (0.28 to 1.36) | 0.230 ^e |

Table 2. Comparison of the vaginal pH and microscopic evaluation between groups before and after treatment. ^aStandard deviation, ^bconfidence interval, ^cindependent samples t-test, ^dANCOVA with adjusting the baseline value, ^ePearson Chi-square.

| Variables | Mycozin (n = 64) N (%) | Clotrimazole (n = 62) N (%) | Odds Ratio (95% Confidence Interval) | P ^a |
|------------------------------|------------------------------|-----------------------------------|---|----------------|
| Complaints | | | | |
| Vaginal odor | | | | |
| Before treatment | 36 (56.3) | 39 (62.9) | 1.32 (0.65 to 2.70) | 0.447 |
| After treatment | 21 (35.0) | 26 (44.1) | 1.46 (0.70 to 3.06) | 0.312 |
| Dysuria | | | | |
| Before treatment | 41 (64.1) | 32 (51.6) | 0.60 (0.30 to 1.22) | 0.157 |
| After treatment | 18 (30.0) | 14 (23.7) | 0.73 (0.32 to 1.64) | 0.440 |
| Urinary frequency | | | | |
| Before treatment | 39 (60.9) | 33 (53.2) | 0.73 (0.36 to 1.48) | 0.382 |
| After treatment | 22 (36.7) | 22 (37.3) | 1.03 (0.49 to 2.16) | 0.944 |
| Itching | | | | |
| Before treatment | 44 (68.8) | 50 (80.6) | 1.90 (0.83 to 4.31) | 0.125 |
| After treatment | 26 (43.3) | 13 (22.0) | 0.37 (0.17 to 0.82) | 0.013 |
| Itching in intercourse | | | | |
| Before treatment | 25 (39.1) | 27 (43.5) | 1.20 (0.60 to 2.45) | 0.609 |
| After treatment | 14 (23.3) | 8 (13.6) | 0.51 (0.20 to 1.34) | 0.170 |
| Lower abdominal pain | | | | |
| Before treatment | 43 (67.2) | 39 (62.9) | 0.83 (0.40 to 1.72) | 0.614 |
| After treatment | 34 (56.7) | 28 (47.5) | 0.69 (0.33 to 1.42) | 0.315 |
| Irritation in intercourse | | | | |
| Before treatment | 34 (53.1) | 37 (59.7) | 1.31 (0.64 to 2.65) | 0.458 |
| After treatment | 12 (20.0) | 14 (23.7) | 1.24 (0.52 to 2.98) | 0.623 |
| Dyspareunia | | | | |
| Before treatment | 34 (53.1) | 39 (62.9) | 1.50 (0.73 to 3.05) | 0.266 |
| After treatment | 29 (48.3) | 20 (33.9) | 0.55 (0.26 to 1.15) | 0.110 |
| Clinical observations | | | | |
| Abnormal cervical appearance | | | | |
| Before treatment | 6 (9.4) | 12 (19.4) | 1.20 (0.56 to 2.60) | 0.109 |
| After treatment | 6 (10.0) | 6 (10.2) | 0.98 (0.30 to 3.24) | 0.976 |
| Vulvo-vaginal erythema | | | | |
| Before treatment | 44 (68.8) | 45 (72.6) | 1.20 (0.56 to 2.59) | 0.637 |
| After treatment | 19 (31.7) | 14 (23.7) | 0.67 (0.30 to 1.51) | 0.333 |
| Abnormal discharge | | | | |
| Before treatment | 64 (100.0) | 62 (100.0) | | |
| After treatment | 33 (55.0) | 26 (44.1) | 1.55 (0.75 to 3.20) | 0.233 |
| Non homogenous discharge | | | | |
| Before treatment | 62 (96.9) | 62 (100.0) | 2.00 (1.68 to 2.39) | 0.496 |
| After treatment | 29 (48.3) | 24 (40.7) | 1.36 (0.66 to 2.81) | 0.401 |
| Color of discharge | | | | |
| Before treatment | | | | |
| Cottage cheese like | 64 (100.0) | 62 (100.0) | | |
| Gray/colorless/ yellow | 0 (0.0) | 0 (0.0) | | |
| After treatment | | | 0.78 (0.38 to 1.62) | 0.510 |
| Cottage cheese like | 28 (46.7) | 24 (40.7) | | |
| Gray/colorless/ yellow | 32 (53.3) | 35 (59.3) | | |
| Discharge appearance | | | | |
| Before treatment | | | | |
| Nontransparent/Frothy | 64 (100.0) | 62 (100.0) | | |
| Transparent | 0 (0.0) | 0 (0.0) | | |
| After treatment | | | 0.64 (0.31 to 1.32) | 0.229 |
| Nontransparent/Frothy | 31 (51.7) | 24 (40.7) | | |
| Transparent | 29 (48.3) | 35 (59.3) | | |
| Vaginal odor | | | | |
| Before treatment | 14 (21.9) | 25 (40.3) | 2.41 (1.11 to 5.27) | 0.025 |
| After treatment | 11 (18.3) | 17 (28.8) | 1.80 (0.76 to 4.27) | 0.862 |
| Continued | | | | |

| Variables | Mycozin (n = 64) N (%) | Clotrimazole (n = 62) N (%) | Odds Ratio (95% Confidence Interval) | P ^a |
|------------------------|------------------------------|-----------------------------------|---|----------------|
| Macroscopic evaluation | | | | |
| Before treatment | 64 (100.0) | 62 (100.0) | | |
| After treatment | 29 (48.3) | 22 (37.3) | 0.64 (0.31 to 1.32) | 0.223 |

Table 3. Comparison of the patient complaints and clinical observations between groups before and after treatment. ^a Pearson Chi-square.

| Variables | Mycozin N = 60 N (%) | Clotrimazole N = 59 N (%) | P ^a |
|-----------------------------------|----------------------------|---------------------------------|----------------|
| Patient improvement | | | 0.074 |
| Very good | 21 (32.8) | 26 (41.9) | |
| Good | 9 (14.1) | 13 (21.0) | |
| Not bad | 17 (26.6) | 15 (24.2) | |
| Bad | 13 (20.3) | 5 (8.1) | |
| Patient satisfaction | | | 0.056 |
| Very satisfied | 21 (32.8) | 26 (41.9) | |
| Satisfied | 9 (14.1) | 13 (21.0) | |
| Equally satisfied and unsatisfied | 14 (21.9) | 15 (24.2) | |
| Unsatisfied | 12 (18.8) | 3 (4.8) | |
| Very unsatisfied | 4 (6.3) | 2 (3.2) | |

Table 4. Comparison of the patient improvement and satisfaction between groups after treatment. ^a Mann-Whitney U.

| Variables | Mycozin N = 60 N (%) | Clotrimazole N = 59 N (%) |
|-------------------------------|----------------------------|---------------------------------|
| Intensification of itching | 4 (6.3) | 1 (1.6) |
| Intensification of irritation | 3 (4.7) | 3 (4.8) |
| Skin redness | 3 (4.7) | 1 (1.6) |
| Skin dryness | 1 (1.6) | 0 (0.0) |

Table 5. Side effects in study groups.

Data availability

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Received: 26 July 2024; Accepted: 23 December 2024

Published online: 18 January 2025

References

- Ryan, K.J., Berkowitz, R.S., Barbieri, R.L. & Dunaif, A.E. *Kistners Gynecology and Women's Health*. Translated by: Ghazi Jahani B, Ghotbi R. 688–690 (Golban Pub, 2006).
- Carr, P. L., Felsenstein, D. & Friedman, R. H. Evaluation and management of vaginitis. *J. Gen. Intern. Med* **13**, 335–346 (1998).
- Shan, Y., Fan, S., Liu, X. & Li, J. Prevalence of *Candida albicans*-closely related yeasts, *Candida africana* and *Candida dubliniensis*, in vulvovaginal candidiasis. *Med. Mycol* **52**, 636–640 (2014).
- Paladine, H. L. & Desai, U. A. Vaginitis: Diagnosis and treatment. *Am. Fam. Physician*. **97**, 321–329 (2018).
- Martinez, R. et al. Improved treatment of vulvovaginal candidiasis with fluconazole plus probiotic *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14. *Lett. Appl. Microbiol* **48**, 269–274 (2009).
- Sangamithra, V., Verma, R., Sengottuvelu, S. & Sumathi, R. Candida infections of the genitourinary tract. *Res. J. Pharm. Technol* **6**, 1111–1115 (2013).
- Farahmand, M., Abedini, M. & Hashemi, Z. Prevalence of vaginitis in Iranian women-Symptoms and clinical association. *Med. Sci. J. Islamic. Azad. Univ. Tehran. Med. Branch* **22**, 62–68 (2012).
- Gonçaves, B. et al. Vulvovaginal candidiasis: Epidemiology, microbiology and risk factors. *Crit. Rev. Microbiol* **42**, 905–927 (2016).
- Dou, N. et al. Risk factors for candida infection of the genital tract in the tropics. *Afr. Health. Sci* **14**, 835–839 (2014).

10. de Cássia Orlandi Sardi, J. et al. Vulvovaginal candidiasis: epidemiology and risk factors, pathogenesis, resistance, and new therapeutic options. *Curr. Fungal. Infect. Rep* **15**, 32–40 (2021).
11. Sasani, E. et al. Vulvovaginal candidiasis in Iran: A systematic review and meta-analysis on the epidemiology, clinical manifestations, demographic characteristics, risk factors, etiologic agents and laboratory diagnosis. *Microb. Pathog* **154**, 104802 (2021).
12. Yang, S. et al. Clinical significance and characteristic clinical differences of cytolytic vaginosis in recurrent vulvovaginitis. *Gynecol. Obstet. Invest* **82**, 137–143 (2017).
13. Berek, J. & Berek, S. *Novak's Gynecology*. Translated by: Ghazi Jahani, B. 3rd Ed. (Golban Publication, 2012).
14. Alahverdi, F., Kheirkhah, M. & Janani, L. Treatment outcomes of vaginal infections on sexual function. *J. Med. Life* **13**, 329 (2020).
15. Alizadeh, S., Namazi, A. & Amini, M. Comparative study of micosin vaginal cream versus miconazole vaginal cream for the treatment of mycotic vaginitis. *Mod. Care. J* **11**, 176–195 (2014).
16. Farshbaf Khalili, A. et al. Comparing the effect of garlic, zataria multiflora and Clotrimazole vaginal cream 2% on improvement of fungal vaginitis: A randomized controlled trial. *Iran. Red. Crescent. Med. J* **18**, 0–0 (2016).
17. Schopf, R. et al. Efficacy and tolerability of terbinafine 1% topical solution used for 1 week compared with 4 weeks clotrimazole 1% topical solution in the treatment of interdigital tinea pedis: A randomized, double-blind, multi-centre, 8-week clinical trial. *Mycoses* **42**, 415–420 (1999).
18. Pappas, P. G., Lionakis, M. S., Arendrup, M. C., Ostrosky-Zeichner, L. & Kullberg, B. J. Invasive candidiasis. *Nat. Rev. Dis. Primers* **4**, 18026 (2018).
19. Sarpong, A.K. Odoi, H. Boakye, Y.D. Boamah, V.E. & Agyare, C. Resistant *C. albicans* implicated in recurrent vulvovaginal candidiasis (RVVC) among women in a tertiary healthcare facility in Kumasi, Ghana. *BMC Womens Health* **19** (24), 412.20 (2024).
20. Agarwal, K. C. Therapeutic actions of garlic constituents. *Med. Res. Rev.* **16**, 111–124 (1996).
21. Chidinma, O., Timothy, O. C., Samuel, S., Isaac, E. & Hauwa, S. Therapeutic effects of garlic: A review. *Sci. J. Biol. Life. Sci.* **1**, 1–5 (2019).
22. Shafaroudi, A.M. Gorji, N.E. Nasiri, P. Javidnia, J. & Saravi, M.E. Antifungal properties of Zataria multiflora on candida species: A systematic review. *J. Evid. Based Integr. Med* **27**, 2515690X221132272 (2022).
23. Moori, H. & Majd, A. The comparison of the effects of micosin vaginal cream (made of garlic) and metronidazole vaginal gel on treatment of bacterial vaginosis. *AMUJ* **13**, 35–44 (2010).
24. Bahadoran, P., Rokni, F. K. & Fahami, F. Investigating the therapeutic effect of vaginal cream containing garlic and thyme compared to clotrimazole cream for the treatment of mycotic vaginitis. *Iran. J. Nurs. Midwifery. Res* **15**, 343 (2010).
25. Khosravi, A. R., Eslami, A. R., Shokri, H. & Kashanian, M. Zataria multiflora cream for the treatment of acute vaginal candidiasis. *Int. J. Gynecol. Obstet* **101**, 201–202 (2008).
26. Sobel, J. D. Epidemiology and pathogenesis of recurrent vulvovaginal candidiasis. *Am. J. Obstet. Gynecol* **152**, 924–935 (1985).
27. Safari, E., Mohammad Alizadeh Charandabi, S., Adibpour, M., Mirghafourvand, M. & Javadzadeh, Y. Comparing the effects of Calendula officinalis and clotrimazole on vaginal Candidiasis: A randomized controlled trial. *Women Health* **57**, 1145–60 (2017).
28. Pandis, N. The chi-square test. *Am. J. Orthod. Dentofac. Orthop.* **1**, 898–899 (2016).
29. Goldberg, D. E. & Scheiner, S. M. ANOVA and ANCOVA: Field competition experiments. *InDesign Anal. Ecol. Exp.* **24**, 69–93 (2020).
30. MacFarland, T.W & Yates, J.M. Mann–Whitney U Test. *Introduction to Nonparametric Statistics for the Biological Sciences Using R.* 103–32 (2016).
31. Lin, Y. P., Chen, W. C., Cheng, C. M. & Shen, C. J. Vaginal pH value for clinical diagnosis and treatment of common vaginitis. *Diagnostics* **11**, 1996 (2021).
32. Watson, C.J. et al. The effects of oral garlic on vaginal candida colony counts: A randomised placebo controlled double-blind trial. *BJOG: Int. J. Obstet. Gy* **121**, 498–506 (2014).
33. Martínez-González, M.C. Goday Buján, J.J. Martínez Gómez, W. & Fonseca Capdevila, E. Concomitant allergic contact dermatitis due to *Rosmarinus officinalis* (rosemary) and *Thymus vulgaris* (thyme). *Contact Dermatitis* **1**(01051873), 56 (2007).
34. Borrelli, F. Capasso, R. & Izzo, A.A. Garlic (*Allium sativum* L.): Adverse effects and drug interactions in humans. *Mol. Nutr. Food Res.* **51**, 1386–1397 (2007).
35. Fouladi, Z., Afshari, P., Gharibi, T. & Dabbagh, M. A. The comparison of Zataria multiflora boiss (Avishan Shirazi) and Clotrimazol vaginal cream in the treatment of candidiasis vaginitis. *Iran. South. Med. J* **12**, 214–224 (2009).
36. Li, W. R. et al. Antifungal activity, kinetics and molecular mechanism of action of garlic oil against *Candida albicans*. *Sci. Rep* **6**, 22805 (2016).
37. Bayat, M., Hassannejad, N. & Ghazanfari, H. Evaluation of intrinsic and acquired immune cells infiltration in kidney and spleen of the mice infected with systemic candidiasis and treated with chloroform fraction of Zataria multiflora Boiss. *Microb. Pathog* **114**, 444–448 (2018).
38. Patel, M., Patel, K., Bera, K. & Prajapati, B. Herbal formulations for the treatment of fungal infection. *Herbal Formul. Phytochem. Pharmacogn.* (Elsevier). 1–20 (2024).

Acknowledgements

We acknowledge the Clinical Research Development Unit of Taleghani Hospital, Tabriz University of Medical Sciences for their scientific support.

Author contributions

KhH, ZA, VR, LM, SM, BSh and MM contributed to the conception, and design of the study. ZA collected data and drafted the manuscript under the direct supervision of MM. LM and SM conducted laboratory tests. MM conducted the statistical analysis. KhH, VR, LM, SM, BSh and MM revised the manuscript. All authors read and approved the final manuscript.

Funding

Tabriz University of Medical Sciences provided funding but it had no role in the design and conduct of the study and decision to this manuscript writing and submission.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The study was approved by the ethics committee of Tabriz University of Medical Sciences, Iran with ethics code of IR.TBZMED.REC.1402.112. The study complies with the World Medical Association Helsinki Declaration regarding the ethical conduct of research involving human subjects. The study protocol was developed following the Consort guidelines for clinical trials and included a completed CONSORT checklist. Written informed consent was obtained from each individual participant. The principles of anonymity and confidentiality were applied and the participants were provided with the results upon their request.

Additional information

Correspondence and requests for materials should be addressed to M.M.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

© The Author(s) 2025