Original Article

Vaginal Royal Jelly for Vulvovaginal Candidiasis Treatment: A Randomized Clinical Trial

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Abstract

Background: Vulvovaginal Candidiasis (VVC) is a prevalent and complex health issue in women. With the rising resistance to synthetic antifungal medications, there is a growing emphasis on exploring natural remedies that minimize disruption to the normal vaginal flora. The goal of this study is to evaluate the efficacy of vaginal Royal Jelly (RJ) compared with clotrimazole for VVC treatment.

Materials and Methods: This single-blind randomized clinical trial was conducted from 2020 to 2022 at Iran University of Medical Sciences hospitals, involving a total of 90 patients diagnosed with vaginal candidiasis. Positive vaginal culture individuals were randomly allocated to receive either vaginal 1000 mg RJ soft gel capsules or (2%) Clotrimazole cream (45 participants per group). Clinical signs, symptoms, and laboratory tests were statistically compared at baseline and ten days post-treatment. The data were analyzed using the independent t-tests, Mann-Whitney, Chi-square, and Wilcoxon tests through SPSS version 22.

Results: After 10 days of treatment, both groups demonstrated a significant decrease in Candida culture results ($P < 0.001$). RJ also positively impacted vaginal symptoms such as itching, discharge, and burning. Moreover, most patients in both groups became asymptomatic post-treatment.

Conclusions: The present study points out the therapeutic effects of vaginal RJ, a novel natural drug for improving VVC.

Keywords: Clotrimazole, royal jelly, vulvovaginal candidiasis

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Introduction

Genital tract infections are among the most common reasons women seek healthcare. Vulvovaginal Candidiasis (VVC) is the second most prevalent cause of vaginitis, affecting about 75% of women at least once during their reproductive years, with a recurrence rate of 40%–50%.[1-3]

A recent study unveiled that among Iranian women, VVC exhibited an overall prevalence of 47%, with *Candida albicans* identified as the predominant causative agent.[4]

Symptoms of this infection include genital itching, vaginal irritation, thick discharge, dysuria, pain during sex, fissures in the

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vulva and perineum, as well as redness around the vagina.[1,2,4] The main diagnostic method for this infection involves a direct examination of vaginal discharge along with a culture.[4,5]

VVC causes considerable discomfort, poses challenges for clinicians, and leads to significant healthcare costs. Research shows that VVC may raise pregnancy risks and increase susceptibility to HIV infection. Therefore, effective preventive measures, including patient education and robust monitoring, are essential.[4]

Oral or topical azoles are effective treatments for uncomplicated VVC. Topical therapy provides symptom relief within hours, with clotrimazole being the widely accessible and commonly used remedy for vaginal candidiasis.[1,6]

Side effects of topical antifungal medications may include itching, foul-smelling vaginal discharge, dysuria, irritation, dermatitis, and genital itching in the partner. The reported adverse effects associated with clotrimazole, an approved treatment for CVV, and the rising problem of drug resistance highlighted the importance of exploring alternative treatments for candidal vaginitis.[2,7,8]

Currently, there is a preference for natural-based drugs that align better with the body, minimizing disruptions to the normal vaginal flora.[1,2]

Royal jelly (RJ) known as a superfood is a gelatinous, cream-colored secretion produced by the mandibular and hypopharyngeal glands of worker bees, valued for its distinctive health benefits.[9,10]

Containing bioactive components such as proteins, sugars, peptides, fatty acids, and phenolics, RJ exhibits a variety of functional properties, including antimicrobial, antioxidant, immunomodulatory, wound healing, anti-aging, anti-cancer, anti-inflammatory, anti-hypertensive, estrogenic, anti-hyperlipidemic, and neurotrophic effects.[11,12] Recent studies indicated its antifungal activity against *Candida albicans* in vitro.[13,14]

A recent study in Iran found that the alcoholic extract of RJ is effective against C. albicans, as demonstrated by minimum inhibitory concentration and minimum fungicidal concentration measured by counting fungal colonies.[13]

Previously, other researchers confirmed that RJ is effective against *Candida albicans* at concentrations of 10% and higher in a laboratory setting.[14]

Although the most common form of using RJ is oral, the efficacy of topical forms of RJ has also been examined in numerous studies.[11,15,16]

Vaginal RJ significantly alleviates sexual and urinary symptoms and enhances the quality of life in postmenopausal women compared to estrogen treatments, according to a 2016 study.[17,18]

While previous research has highlighted the topical benefits and antifungal properties of RJ, there is a lack of studies on its specific effects on human vaginal candidiasis. This study aims to assess the effectiveness of vaginal RJ compared to clotrimazole in treating VVC.

Materials and Methods

Study design

This randomized, single-blind clinical trial was conducted on 90 patients with vaginal candidiasis at the women's health clinics of Iran University of Medical Sciences hospitals, including Rasoul Akram, Akbar Abadi, and Firoozgar hospitals between March 2021 and 2022. Gynecologists enrolled participants according to inclusion and exclusion criteria during clinical visits.

Inclusive and exclusive criteria

Inclusion criteria involved married women aged 18 to 45 with regular menstrual cycles, diagnosed with vaginal candidiasis through clinical examinations and positive vaginal secretion cultures confirmed by specialists. Pregnant or breastfeeding women, those with a history of allergic sensitivity to vaginal RJ and clotrimazole, patients with immune insufficiency, organ transplant recipients, cancer patients, individuals with liver and kidney failure, and other infectious diseases, and those with a history of receiving antifungal and antibiotic drugs, as well as drug-resistant fungal and bacterial infections were excluded. This study has been aligned with the CONSORT 2010 checklist.[19]

Statistical analysis

Sample size estimation

Each group had a minimum sample size of 45 patients, based on a post-treatment Candida culture average of 150 (CFU/ml) for the RJ group and an expected mean difference of 5 between groups. Statistical parameters were set with Alpha at 0.05 and Beta at 0.8.[20]

Statistical methods

Data normality was evaluated using the Kolmogorov-Smirnov test. Statistical comparisons of mean data were conducted through independent t-tests, Mann-Whitney tests, Chi-square tests, and Wilcoxon tests, utilizing SPSS software (version 22), with a confidence level of $P < 0.05$.

Randomization

In this single-blind (physician-blind) clinical trial, convenient sampling was used, and participants were randomly assigned to receive either RJ or clotrimazole. The randomization was done through a permuted block method with a block size of 4.

Intervention

Before the intervention, eligible participants received explanations about the study objectives and the benefits of using vaginal medications, and all provided informed consent. Particularly, there were no costs associated with patient visits and medications, and they were ensured of data confidentiality.

Initially, confirmation of vaginal candidiasis was achieved through symptoms, clinical examinations, and culture for all participants. To gather personal and medical information, a checklist covering demographics, symptoms, and observations was used. This checklist recorded age, BMI, vaginal candidiasis symptoms (itching, discharge, burning), and past medical history. Before the intervention, a Pap smear was conducted in both groups for screening. Each checklist was assigned a numerical code without the patient's name. The clinic secretary recorded participant information along with their relevant codes. All eligible patients with positive vaginal cultures were randomly and equally allocated to RJ or clotrimazole group (45 patients in each group) [Figure 1].

Individuals in the intervention group were administered Health Aid Tong Fort capsules containing 1000 mg of natural, and pure RJ daily vaginally for ten days. These soft gel capsules are manufactured by Omid Parsina Damavand Company (Tehran, Iran) and obtained the license of the Iranian Food and Drug Organization (FDO) under IRC " 9900852972153155". In the control group, participants were treated with Clotrimazole Vaginal Cream (2%) from Iran Najo Pharmaceutical company (Tehran, Iran) with one full applicator daily for ten days. Patients were also instructed to refrain from using additional vaginal medications and antibiotics and to avoid unprotected sexual activity. At the end of the treatment course, they were reevaluated by physicians.

Outcomes

At the beginning of the study, participants completed a questionnaire with yes/no questions and underwent a vaginal examination to assess VVC symptoms, such as discharge and itching. A Pap smear was performed, and vaginal secretions were tested for pH levels using a strip gauge to rule out other microorganisms.

Normally, the vaginal pH in women with Candida infection falls within the normal range from 4 to 4.5. Vaginal samples for culture on Sabourad's Dextrose Agar with Chloramphenicol Medium were collected from the lateral wall with a cotton-tipped swab.[1,21,22] Following treatment completion, patients underwent clinical examinations, and a second culture was conducted to confirm their former status. All outcomes results were recorded in the observation checklist.

Results

In this study of 90 participants, the mean (SD) age and body mass index for the RJ group were 36.5 ± 7 years and 27.06 ± 3 kg/m², while for the clotrimazole group, they were 35.86 ± 8 years and 27.1 ± 3 kg/m². No significant differences were found between the groups ($P = 0.602$ and $P = 0.948$). Moreover, the differences in education, medical history, and Pap smear results between the two groups were not significant ($P > 0.05$) [Table 1].

After 10 days of therapy, Candida culture results were 132.63 ± 19.77 in the intervention group and 84.76 ± 11.07 in the control group, with this difference being statistically significant ($P = 0.003$), consistent with pre-treatment findings ($P = 0.005$).

Regarding the changes in Candida culture from the baseline to the end of the therapy, a significant decreasing trend was observed in both groups ($P < 0.001$) [shown in Figure 2 and Table 2].

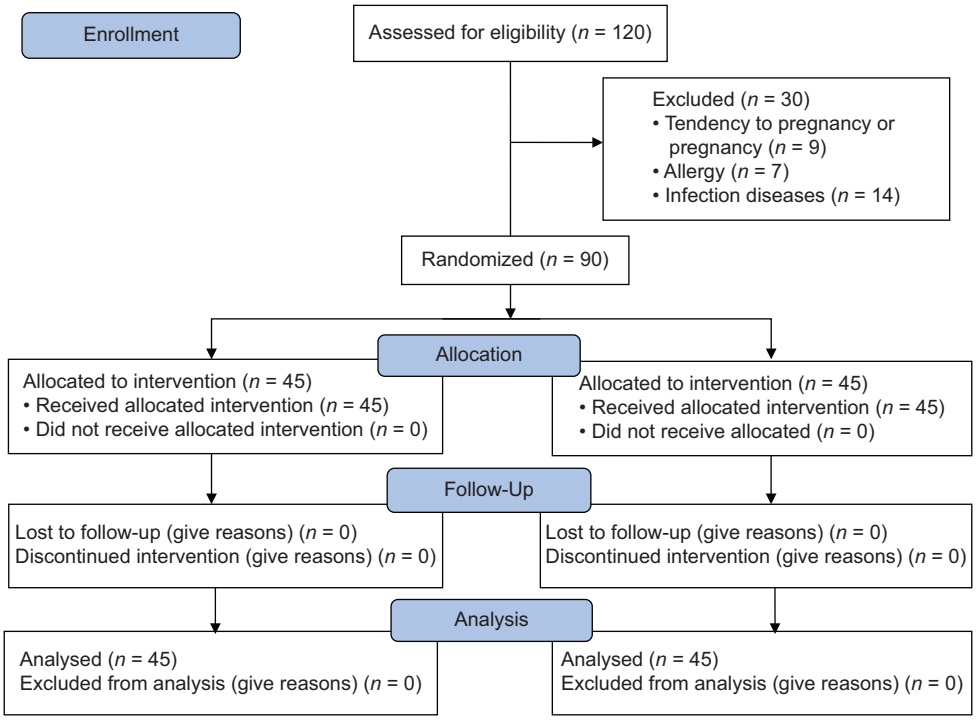

Figure 1: CONSORT diagram showing patient flow

Before the intervention, symptoms of VVC, including itching, burning, and discharge, were assessed in both groups, with no statistically significant differences noted ($P = 0.25$, $P = 0.06$, $P = 0.39$). Most patients in both groups became asymptomatic after treatment, with 37 in the RJ group and 39 in the Clotrimazole group. Vaginal discharge was the most common persistent symptom in a few patients. However, there was no statistically significant difference between the groups regarding VVC symptoms post-intervention ($P > 0.05$). [Table 3].

Discussion

The findings of this randomized, single-blind clinical trial demonstrated a significant reduction in Candida culture results with vaginal RJ soft gel compared to clotrimazole cream. Both treatments positively impacted candidal vaginitis by alleviating symptoms such as itching, discharge, and burning, leading to most patients becoming asymptomatic. However, comparative analysis revealed no statistically significant difference between the two groups. Thus, it can be concluded that RJ and clotrimazole have comparable effects in alleviating symptoms of vaginal candidiasis.

Several studies have been conducted to investigate the efficacy of natural products derived from honeybees on vaginal candidiasis.[2,22,23]

Recently, a randomized clinical trial in Iran compared honey gel and clotrimazole for treating VVC. The research revealed a decrease in vaginal discharge in the honey group, while no change was observed in the clotrimazole group. Furthermore, there was no remarkable difference between the two groups in terms of vulva sensitivity and burning.[23]

In line with the current study, their findings, except for discharge, showed no notable distinction between the two groups in other symptoms associated with vaginal candidiasis, both before and after treatment.

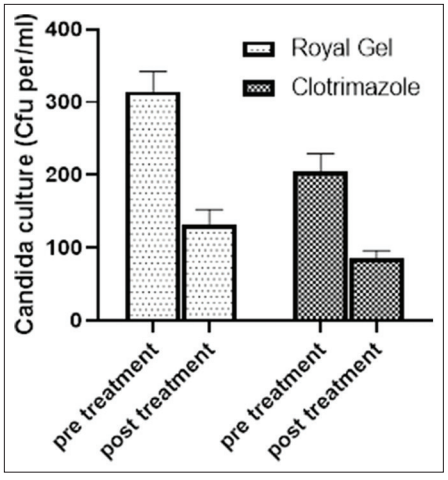

Figure 2: Average colony counts of fungi in two groups

However, in the present research, unlike the preceding one, RJ caused a statistically significant alteration in the mean of Candida culture compared to clotrimazole.

In another study, Norouzi Allahleh Korabi, M *et al*.,[22] noted that after seven nights of treatment with vaginal Nigella sativa-Honey or clotrimazole, symptoms of VVC, including

Table 1: Comparative analysis of demographic and clinical data for patients in the clotrimazole and royal gel groups (Data are represented as mean±standard deviation)

Variables	Royal Jelly (*n*=45)	Clotrimazole (*n*=45)	*P*
Age (year)	36.5±7	35.86±8	0.602*
BMI (kg/m^2)	27.06±3	27.1±3	0.948†
Education			
Housewife (*n*%)	9 (20%)	13 (28.9%)	0.707‡
Diploma (*n*%)	18 (40%)	18 (40%)	
Bachelor's degree (*n*%)	14 (31.1%)	10 (22.2%)	
Master's degree (*n*%)	4 (8.9%)	4 (8.9%)	
Past Medical History			
Diabetes (*n*%)	3 (6.7%)	1 (2.2%)	0.308‡
Heart problem (*n*%)	1 (2.2%)	2 (4.4%)	0.500‡
Hypothyroidism (*n*%)	1 (2.2%)	3 (6.7%)	0.500‡
Nothing (*n*%)	39 (86.7%)	39 (86.7%)	0.923‡
Pap Smear			
Normal (*n*%)	38 (84.4%)	40 (88.9%)	0.37‡
Inflammatory (*n*%)	7 (15.6%)	5 (11.1%)	

*Tested by Independent *t*-test. †Tested by Mann-Whitney test. ‡Tested by Chi-square test

Table 2: Comparative analysis of average Candida cultures in patients from the clotrimazole and royal jelly groups (Data are represented as Mean±Standard Deviation)

Candida culture (Cfu/ml)	Royal Jelly (*n*=45)	Clotrimazole (*n*=45)	*P*
Pretreatment	314.955±27.09	205.575±23.63	0.005†
Posttreatment	132.63±19.77	84.755±11.065	0.003†
	<0.001**	<0.001**	

†Tested by Mann-Whitney test. **Tested by Wilcoxon test

Table 3: Comparative analysis of VVC symptoms in RJ and Clotrimazole groups before and after the intervention

Symptoms	Royal Jelly (*n*=45)	Clotrimazole (*n*=45)	*P*‡
Before treatment			
Itching	18 (56.2%)	14 (43.8%)	0.25
Discharge	15 (39.5%)	23 (60.5%)	0.06
Burning	12 (55.6%)	8 (44.4%)	0.39
Nothing	0	0	0
After treatment			
Itching	2 (66.7%)	1 (33.3%)	0.50
Discharge	3 (42.9%)	4 (57.1%)	0.50
Burning	3 (75%)	1 (25%)	0.30
Nothing	37 (48.7%)	39 (51.3%)	0.38

‡Tested by Chi-square test

discharge, redness, and itching, as well as fungal culture, improved in both groups. The findings of this study aligned with the results of the current trial.

Similarly, a 2021 study reported significant improvement in VVC symptoms in both the Nika group (a blend of honey, propolis, and olive) and the Clotrimazole vaginal cream group after the intervention. By the end of the study, most women, especially in the Nika group, had negative *Candida albicans* cultures.[2]

All the mentioned studies have focused on the effectiveness of bee products such as honey and propolis for managing candidal vaginitis. This current study introduces a novel survey of the efficacy of another valuable bee product, RJ, uniquely.

Research has been widely conducted to explore the health-enhancing advantages and pharmaceutical properties of RJ, a creamy substance produced by worker bees, such as anti-inflammatory, antimicrobial, antioxidant, healing injuries, and modulating the immune system activities from animal models to human studies.[10-12] Its antifungal effects, particularly against Candida albicans—the most common fungal pathogen responsible for vaginal candidiasis in humans—have been the subject of *in vitro* investigation.[12-14]

A notable aspect of the present study is that, for the first time, oral RJ capsules have shown efficacy in treating vaginal candidiasis when used in the form of a suppository.

This study has several limitations, including a relatively small sample size and a short follow-up period. Furthermore, the identification of Candida species was not conducted because of high costs. Therefore, further research is needed to assess the effects of RJ on various Candida species with a larger participant pool. It is also important to highlight that, despite its many therapeutic applications in Iran, RJ is not an inexpensive product.

Conclusions

This study highlights the therapeutic efficacy of vaginal RJ in treating VVC, with no adverse effects reported by participants. Future research should investigate the effects of RJ on other vaginal infections and clarify its mechanism of action. Such studies could facilitate the development of an RJ vaginal formulation in the pharmaceutical industry.

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Ethics approval and consent to participate

The trial adhered to the Declaration of Helsinki received Ethics Committee approval from the Iran University of Medical Sciences (IR.IUMS.FMD.REC.1399.865), and was registered with the Iranian Registry of Clinical Trials (IRCT20220210053988N1). Written informed consent was obtained from patients before enrollment.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Jaldani S, Fatahinia M, Maraghi E, Moghimipour E, Javadnoori M. Comparison of the effectiveness of Satureja khuzestanica and clotrimazole vaginal creams for the treatment of vulvovaginal candidiasis. J Med Life 2021;14:111-7.
2. Parsapour H, Masoumi SZ, Shayan A, Moradkhani S, Ghiasian SA, Rashidi MK. Comparison of the effects of nika vaginal cream with clotrimazole cream on vaginal candidiasis symptoms: A randomized single-blind clinical trial. Iran J Nurs Midwifery Res 2021;26:521-5.
3. Nyirjesy P, Brookhart C, Lazenby G, Schwebke J, Sobel JD. Vulvovaginal candidiasis: A review of the evidence for the 2021 centers for disease control and prevention of sexually transmitted infections treatment guidelines. Clin Infect Dis 2022;74:S162-s8.
4. Sasani E, Rafat Z, Ashrafi K, Salimi Y, Zandi M, Soltani S, *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 2021;154:104802.
5. Yano J, Sobel JD, Nyirjesy P, Sobel R, Williams VL, Yu Q, *et al*. Current patient perspectives of vulvovaginal candidiasis: Incidence, symptoms, management and post-treatment outcomes. BMC Womens Health 2019;19:1-9.
6. Napolitano M, Cappello M, Festa B, Patruno C. Clotrimazole-related allergic contact dermatitis. G Ital Dermatol Venereol 2020;155:355-7.
7. Corazza M, Scuderi V, Toni G, Forconi R, Zedde P, Borghi A. Severe vulvovaginal allergic contact dermatitis due to clotrimazole contained in multiple topical products. Contact Dermatitis 2020;82:57-9.
8. Khalilzadeh S, Eftkhar T, Shirbeigi L, Tabarrai M, Toliyat T, Fayazmanesh S, *et al*. Efficacy of a vaginal tablet as a Persian medicine product on vulvovaginal candidiasis: A double-blind, randomised, placebo-controlled trial. Pharm Biol 2020;58:574-80.
9. Ahmad S, Campos MG, Fratini F, Altaye SZ, Li J. New insights into the biological and pharmaceutical properties of royal jelly. Int J Mol Sci 2020 8;21:382.
10. Pasupuleti VR, Sammugam L, Ramesh N, Gan SH. Honey, propolis, and royal jelly: A comprehensive review of their biological actions and health benefits. Oxid Med Cell Longev 2017;2017:1259510.
11. Siavash M, Shokri S, Haghighi S, Shahtalebi MA, Farajzadehgan Z. The efficacy of topical royal jelly on healing of diabetic foot ulcers: A double-blind placebo-controlled clinical trial. Int Wound J 2015;12:137-42.
12. Ahmad S, Campos MG, Fratini F, Altaye SZ, Li J. New insights into the biological and pharmaceutical properties of royal jelly. Int J Mol Sci 2020;21:382.
13. Moghim H, Taghipour S, Kheiri S, Khabbazi H, Baradaran A. Antifungal effects of Iranian propolis extract and royal jelly against candida albicans in-vitro. Int J Prev Med 2021;12:163.
14. Günalp R, Ulusoy M, Çelebier I, Keskin N. Antifungal effect of royal jelly on Candida albicans. J Biotech 2018;280:S70-1.
15. Seyyedi F, Rafiean-Kopaei M, Miraj S. Comparison of the effects of vaginal royal jelly and vaginal estrogen on quality of life, sexual and urinary function in postmenopausal women. J Clin Diagn Res 2016;10:Qc01-5.
16. Yamauchi K, Kogashiwa Y, Moro Y, Kohno N. The effect of topical application of royal jelly on chemoradiotherapy-induced mucositis in head and neck cancer: A preliminary study. Int J Otolaryngol

2014;2014:974967.
17. Seyyedi F, Kopaei MR, Miraj S. Comparison between vaginal royal jelly and vaginal estrogen effects on quality of life and vaginal atrophy in postmenopausal women: A clinical trial study. Electron Physician 2016;8:3184-92.
18. Seyyedi F, Rafiean-Kopaei M, Miraj S. Comparison of the effects of vaginal royal jelly and vaginal estrogen on quality of life, sexual and urinary function in postmenopausal women. J Clin Diagn Res 2016;10:QC01.
19. Schulz KF, Altman DG, Moher D, the CG. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. BMC Med 2010;8:18.
20. Rosner B. Fundamentals of Biostatistics. 8th ed: Cengage Learning; United States, 2015.
21. Marot-Leblond A, Nail-Billaud S, Pilon F, Beucher B, Poulain D, Robert R. Efficient diagnosis of vulvovaginal candidiasis by use of a new rapid immunochromatography test. J Clin Microbiol 2009;47:3821-5.
22. Norouzi Allahleh Korabi M, Mirmolaei ST, Tabarrai M, Ghalandarpoor-Attar SM, Sadati Lamardi SN, Haghani S. Comparison between the efficacy of nigella sativa-honey and clotrimazole on vulvovaginal candidiasis: A randomized clinical trial. Evid Based Complement Alternat Med 2022;2022:1739729.
23. Seifinadergoli Z, Nahidi F, Safaiyan A, Javadzadeh Y, Eteraf Oskouei T. Comparison of the efficacy of honey gel and clotrimazole cream in the treatment of vaginal candidiasis signs: A randomized clinical trial. J Caring Sci 2020;9:162-7.