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Comparison of Fluconazole with Oral Probiotic and Fluconazole in the Treatment of Vulvovaginal Candidiasis : A Systematic Review And Meta-Analysis Of RCT Studies

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ABSTRAK

Vulvovaginal candidiasis, a common fungal infection that affects up to 75% of women at least once in their lifetime. With increasing resistance to azole antifungals, such as fluconazole, due to factors such as gene efflux pumps, alternative treatments are needed. Probiotics, specifically Lactobacillus species, have emerged as a promising option due to their ability to inhibit *Candida albicans* and modulate the host immune response. This study analyzed data from randomized controlled trials. We collected data from articles comparing probiotics with fluconazole therapy and fluconazole alone with or without placebo in patients with vulvovaginal candidiasis published between 2009 and 2024. We obtained articles from scientific databases such as Scopus, Pubmed, ScienceDirect, Clinical Key, JSTOR and Google Scholar based on inclusion criteria. Data analysis was performed using Review Manager Version 5.4.1. The results showed that probiotics significantly reduced symptoms of vaginal discharge (OR value = 0.14 (0.07,0.29), 95% CI) and improved culture test results (OR value = 0.33 (0.17,0.63), 95% CI), indicating potential benefits in improving vaginal microbiota balance and preventing recurrent infections. However, probiotics did not significantly relieve other symptoms, such as itching (OR value = 0.67 (0.27,1.61), 95% CI), irritation (OR value = 0.56 (0.25,1.24), 95% CI), and dyspareunia (OR value = 0.91 (0.34,2.43), 95% CI). For individuals with vulvar candidiasis who are unresponsive to fluconazole therapy, probiotic drugs can be given as additional therapy.

Keywords: probiotic, adjuvant therapy, Lactobacillus, vulvovaginal candidiasis

ABSTRAK

Kandidiasis vulvovaginal, infeksi jamur umum yang menyerang hingga 75% wanita setidaknya sekali dalam hidup mereka. Dengan meningkatnya resistensi terhadap antijamur azole, seperti flukonazol, karena faktor-faktor seperti pompa efluks gen, diperlukan pengobatan alternatif. Probiotik, khususnya spesies Lactobacillus, telah muncul sebagai pilihan yang menjanjikan karena kemampuannya untuk menghambat *Candida albicans* dan memodulasi respons imun inang. Studi ini menganalisis data dari uji coba terkontrol acak. Kami mengumpulkan data dari artikel yang membandingkan probiotik dengan terapi flukonazol dan flukonazol saja dengan atau tanpa plasebo pada pasien dengan kandidiasis vulvovaginal yang diterbitkan antara tahun 2009 dan 2024. Kami memperoleh artikel dari basis data ilmiah seperti Scopus, Pubmed, ScienceDirect, Clinical Key, JSTOR dan Google Scholar berdasarkan kriteria inklusi. Analisis data dilakukan dengan menggunakan Review Manager Versi 5.4.1. Hasil penelitian menunjukkan bahwa probiotik secara bermakna menurunkan gejala keputihan (nilai OR = 0,14 (0,07,0,29), 95% CI) dan memperbaiki hasil uji kultur (nilai OR = 0,33 (0,17,0,63), 95% CI), yang menunjukkan potensi manfaat dalam memperbaiki keseimbangan mikrobiota vagina dan mencegah infeksi berulang. Namun, probiotik tidak secara bermakna meredakan gejala lain, seperti gatal (nilai OR = 0,67 (0,27,1,61), 95% CI), iritasi (nilai OR = 0,56 (0,25,1,24), 95% CI), dan dispareunia (nilai OR = 0,91 (0,34,2,43), 95% CI). Bagi individu dengan kandidiasis vulva yang tidak responsif terhadap terapi flukonazol, obat probiotik dapat diberikan sebagai terapi tambahan.

Kata kunci: probiotik, terapi tambahan, Lactobacillus, kandidiasis vulvovaginal

I. INTRODUCTION

1. Background

Vulvovaginal candidiasis (VVC) is a vaginal infection caused by fungi, most commonly *Candida albicans*. It affects up to 75% of women so women experience this infection at least once in their lifetime, with a recurrent risk of 5-8%.(1–5) Many things influence the occurrence of this infection including pregnancy, diabetes, immunosuppression, and antibiotic use. Candida species form biofilms, which contribute to drug resistance and recurrence. Several influencing virulence factors such as candidalysin, secreted aspartyl protease, and lipase also play a role in pathogenesis.(4,6–8) The first-line management of VVC is the use of azole antifungals such as fluconazole, itraconazole, and others. However, the increasing use of azoles that are not in accordance with the rules increases the risk of resistance in women with VVC. The mechanism of azole resistance also involves gene efflux pumps such as MDR1 and CDR1 CDR2 genes.(9–14) With the increasing risk of resistance to azole preparations, it encourages scientists to look for alternative treatments that are effective for managing VVC. There are several natural compounds that have now been developed as alternatives to replace or complement azole therapy such as essential oils, probiotics, plant extracts, etc. In addition to natural compounds, research has also developed other medicinal compounds such as ibrexafungerp, which according to claims can currently treat VVC patients who experience resistance to azole preparations.(15–19) Vulvovaginal candidiasis can be treated with the help of probiotic bacteria, such as the Lactobacillus species. They can prevent the development of *Candida albicans* and its hyphal formation. This can be achieved by the production of various antimicrobial compounds, such as hydrogen peroxide and bacteriocins.(20–23) In addition, probiotics can modulate the host immune response, increasing the activity of immune cells such as neutrophils and natural killer T cells against Candida infection. Probiotic-derived compounds, such as cell-free culture supernatants, have also shown direct anti-Candida activity. Compared with conventional antifungal treatments, probiotics offer a more natural and potentially safer alternative, especially in cases of recurrent or drug-resistant VVC. Clinical studies have reported successful outcomes when probiotics are used as an adjunct or alternative therapy to VVC. The evidence suggests that probiotics, particularly Lactobacillus species, may be a valuable adjunct to the management of vulvovaginal candidiasis, either as a stand-alone treatment or in combination with conventional antifungal therapy.(20–26) The aim of this systematic review and meta-analysis is to assess the effectiveness of probiotic use in reducing clinical symptoms caused by VVC in several randomized controlled trial studies, so it is hoped that this review can provide valuable information regarding its application in the future.

2. Problem formulation

The formulation of the problem in this study is how to conduct research on Comparison of Fluconazole with Oral Probiotic and Fluconazole in the Treatment of Vulvovaginal Candidiasis : A Systematic Review And Meta-Analysis Of RCT Studies.

3. Research purpose

This research aims to obtain research results from the title Comparison of Fluconazole with Oral Probiotic and Fluconazole in the Treatment of Vulvovaginal Candidiasis : A Systematic Review And Meta-Analysis Of RCT Studies.

4. Benefit of Research

Benefits of research is to obtain results and implications and implementation of the research title Comparison of Fluconazole with Oral Probiotic and Fluconazole in the Treatment of Vulvovaginal Candidiasis : A Systematic Review And Meta-Analysis Of RCT Studies.

II. METHOD

Protocol

This evaluation was carried out according to the PRISMA 2020 protocol.

Data source

The systematic review and meta-analysis were carried out according to the Systematic Reviews and Meta-Analyses (PRISMA) Reporting Items. We designed a search strategy that targets multiple randomized clinical trials by using controlled vocabulary, including terms such as "Medical Subject Headings" which are based on spelling variants, truncation, and synonyms. We also use Boolean operators and field labels that are adapted for different search engines, without restrictions. The following databases were searched using the strategy. From January 2012 to November 2024, various search engines such as Scopus, PubMed, JSTOR, Science Direct, Google Scholar, and Clinical Key, were used to look for English language publications. Figure 1 shows the search strategies that were used.

Search strategy

Different search terms were used, such as "probiotic", "natural antifungal", "triazole", "antifungal", “vulvovaginal candidiasis”. The results were then refined using Boolean operators. The strategy was restricted to studies that were published in English.

Quality assessment and study selection

Two authors were assigned to evaluate all the articles that were found in these databases. They then checked the titles, abstracts, and full texts of the articles before excluding unrelated studies. The disagreements among the selected papers were resolved through discussions and interaction with the third author.

Eligibility criteria

Studies were included in the review based on the following criteria:

Inclusion criteria:

Population	:	Studies involving women diagnosed with VVC
Intervention	:	Studies examining antifungal treatments derived from probiotic or probiotic combination with conventional antifungal (e.g., azole)
Comparator	:	Studies comparing conventional antifungal (e.g., azoles) or conventional antifungal with placebo
Outcome	:	Studies reporting on efficacy (symptom relief, reduction in culture test) of the interventions.
Study design	:	Randomized controlled trials (RCTs) or clinical trial.
Publication type	:	Peer-reviewed journal articles, full-text available
Language	:	English
Publication date	:	Studies published within the last 12 years.

Data collection process and extraction

The review authors, independently extracted the data from the included studies using a procedure that was previously tested: author, year, country, study design, population, intervension, comparison, and outcome..

III. RESULT AND DISCUSSION

Literature search results

A literature search was conducted with the aim of identifying relevant abstracts from various databases. The search results revealed a total of 16,777 papers from Scopus, PubMed, Science Direct, Clinical Key, JSTOR, and Google Scholar. Duplication filtering

was performed after all the initial data was collected. Of the 16,777 papers, 6,895 were screened for duplicates, while 1,211 articles were not eligible for the automated tool and 11 articles were not in English. This left 8,660 papers that were then further evaluated based on title and abstract to determine their relevance. From the screening results, there were 7,348 papers that were not relevant to the inclusion criteria and 189 papers that were not open access. The next step was a thorough screening of the remaining papers based on PICO (Population, Intervention, Comparison, Outcome) criteria, resulting in 549 irrelevant papers, 566 papers did not have a randomised controlled trial study design, and 3 papers did not clearly state the outcome. Only those with the highest relevance were included in the analysis. Of the 5 that met the inclusion criteria, 4 were included in the meta-analysis. The screening process ensured that only the best papers were included in the review. Figure 1 shows the steps involved in article selection and literature search. The flowchart shows the different phases of the process, such as eligibility, screening, and inclusion. The systematic approach used for the review ensures that the results are credible and meet the high standards expected by top-ranked academic journals..

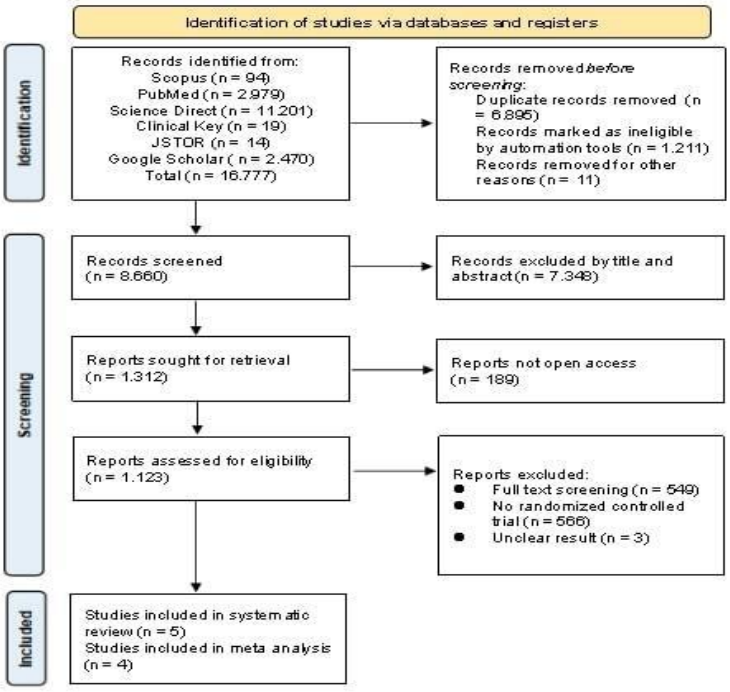

Figure 1. PRISMA flow chart. The flow diagram of the procedure for searching and selecting literature.

Risk of bias considered in included studies

Study was categorized as low risk of bias (Figure 2)

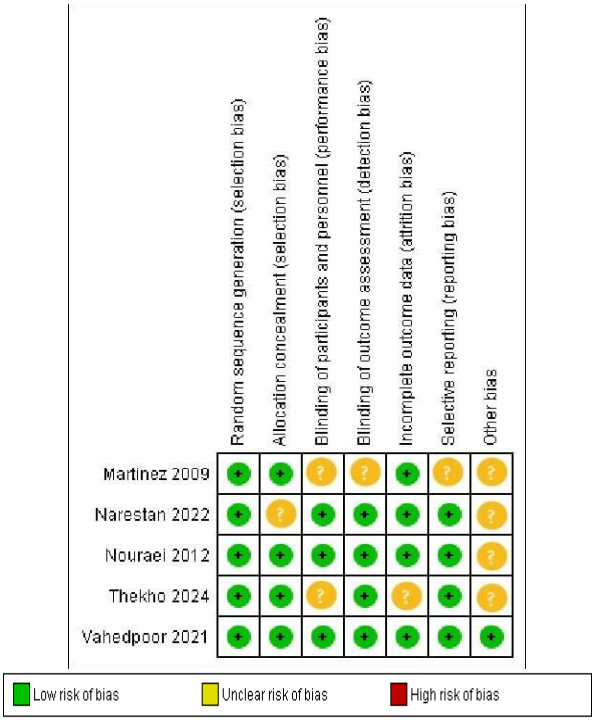

Figure 2. The quality of the included studies was evaluated using the Cochrane assessment of bias tool.

Study characteristics

There were 5 randomised controlled trials of treating patients with VVC using probiotics and conventional azole class antifungals. Of these 5, 4 randomised controlled trials intervened by administering a conventional antifungal plus probiotics with a control conventional antifungal (fluconazole) with or without a placebo, while 1 randomised controlled trial used probiotics alone as the intervention and fluconazole as the control. Of these 5 trials, 1 was excluded because it used a different intervention to the other 4 and the results could not be pooled.

Discussion

This review analyzed 5 papers with 4 of them conducted meta-analysis with RCT study design, which included 291 women with vulvovaginal candidiasis with details of 153 interventions with antifungal fluconazole plus probiotics and 138 acting as a control group with fluconazole with or without placebo. The increasing number of studies on the comparison of the effectiveness of fluconazole administration without or with probiotics since the last 15 years and most of them were conducted in Iran. The results of a meta-analysis conducted on 4 RCT studies showed that the addition of probiotics to fluconazole antifungal therapy provided significant benefits in reducing symptoms of vaginal discharge and reducing positive culture test results in VVC patients. Studies have shown that the addition of probiotic therapy can help relieve symptoms of vaginal discharge caused by bacterial vaginosis and candidiasis. This study also showed that the administration of probiotic strains, such as Lactobacillus species, can improve the balance of vaginal microbiota.(27–30) The effect of consuming probiotic strains on the development and maintenance of vaginal conditions is explained by their ability to stimulate immune responses and eliminate pathogenic bacteria. They can also help maintain a healthy environment by increasing Lactobacilli colonization.(31–35) In addition to reducing

symptoms, the addition of probiotic strain therapy can also help prevent recurrent infections. This suggests that this therapy can be an effective addition to the treatment of women with compromised vaginal health.(27,34,36). The results of this meta-analysis also found that the addition of probiotics to fluconazole antifungal therapy, although there was a tendency to reduce some clinical symptoms (itching, irritation and dyspareunia), the effect was not statistically significant (OR values included 1), the existing evidence is not strong enough to state its effectiveness. In itching and dyspareunia, low or even undetectable heterogeneity was obtained (I2 = 0% for itching and I2 = 19% for dyspareunia) indicating that the results of the studies analyzed were very consistent. While in irritation, high heterogeneity was obtained (I2 = 74%) indicating that there was quite a large variation between studies that needed further study. This variation could be caused by differences in the study population, the dose of probiotics used, or the method of symptom assessment. Therefore, although there is an indication of the potential benefits of probiotics, these results should be interpreted with caution, and further research is needed to confirm these findings and understand the factors that may influence the results. The findings of this meta-analysis show that adding probiotics to standard therapy for patients with VVC infection could help improve the quality of life and reduce the symptoms of the condition. Although this method did not show a significant benefit, there is evidence supporting the use of this supplement in improving culture results and reducing vaginal discharge. The use of probiotics in clinical practice may be focused on patients who are not responding well to standard antifungal therapy or are looking for a more natural treatment method. Although these results are encouraging, it is important to remember that the decisions made in clinical practice should be based on the individual patient's medical history and other factors. Although the results of this meta-analysis support the use of probiotics in treating patients with VVC infection, further studies are needed to confirm the effectiveness of this supplement. The limited number of studies included in the meta-analysis is one of the major limitations of this study, especially in meta-analyses assessing dyspareunia. This limitation may affect the statistical power and generalizability of the analysis. Furthermore, variations in study design, such as duration of treatment, probiotic dosage, and population characteristics, may add undetected heterogeneity. Although the heterogeneity observed in most of the results was low, these factors may still affect the interpretation of the conclusions. Publication bias may also affect the results. For example, if the results of a study are positive, then the authors may have overestimated the effects of probiotics on various outcomes. Another factor that may affect the results is the use of different probiotic strains. Additional studies with a uniform design and involving larger groups are needed to confirm the findings. Further studies on the effects of probiotics in treating patients with VVC infection should also include subgroup analyses to gain a deeper understanding of their impact.

IV. CONCLUSION

In conclusion, this review highlights the potential benefits of adding probiotics to fluconazole antifungal therapy for women with vulvovaginal candidiasis (VVC). The meta-analysis of four randomized controlled trials (RCTs) demonstrated that probiotics can significantly reduce symptoms such as vaginal discharge and improve culture test results, although their effect on other clinical symptoms like itching, irritation, and dyspareunia was not statistically significant. For individuals with vulvar candidiasis who do not respond to fluconazole therapy, probiotic drugs can be given as an additional therapy.

REFERENCES

Abe M, Kinjo Y, Sadamoto S, Shinozaki M, Nagi M, Shibuya K, et al. A-Galactosylceramide-Stimulated Invariant Natural Killer T-Cells Play a Protective Role in Murine Vulvovaginal Candidiasis by Candida Albicans. PLoS One. 2021;16(11):e0259306.

Akimoto-Gunther L, Mendonca P, Takahachi G, Irie MMT, Miyamoto SK, Consolaro MEL, et al. Highlights Regarding Host Predisposing Factors to Recurrent Vulvovaginal Candidiasis: Chronic Stress and Reduced Antioxidant Capacity. PLoS One. 2016;11(7):e0158870.

Alvendal C, Mohanty S, Bohm-Starke N, Brauner A. Anti-Biofilm Activity of Chlorhexidine Digluconate Against Candida Albicans Vaginal Isolates. PLoS One. 2020;15(9):e0238428.

Dias LB, Melhem, Szeszs MW, Filho JM, Hahn RC. Vulvovaginal Candidiasis in Mato Grosso, Brazil: Pregnancy Status, Causative Species and Drugs Tests. Brazilian Journal of Microbiology. 2011;42(4):1300–7.

Khan A, Azam MA, Allemailem KS, Almatroudi A, Alhumaydhi FA, Ahmad HI, et al. Coadministration of Ginger Extract and Fluconazole Shows a Synergistic Effect in the Treatment of Drug-Resistant Vulvovaginal Candidiasis. Infect Drug Resist. 2021;Volume 14:1585–99.

Lotfali E, Erami M, Fattahi M, Nemati H, Ghasemi Z, Mahdavi E. Analysis of Molecular Resistance to Azole and Echinocandin in Candida Species in Patients With Vulvovaginal Candidiasis. Curr Med Mycol. 2022;

Noori M, Dakhili M, Sepahvand A, Davari N. Evaluation of Esterase and Hemolysin Activities of Different Candida Species Isolated From Vulvovaginitis Cases in Lorestan Province, Iran. Curr Med Mycol. 2017;3(4):1–5.

Nyirjesy P, Schwebke JR, Angulo D, Harriott IA, Azie N, Sobel JD. Phase 2 Randomized Study of Oral Ibrexafungerp Versus Fluconazole in Vulvovaginal Candidiasis. Clinical Infectious Diseases. 2021;74(12):2129–35.

Pfavayi LT, Denning DW, Baker S, Sibanda E, Mutapi F. Determining the Burden of Fungal Infections in Zimbabwe. Sci Rep. 2021;11(1).

Qin F, Wang Q, Zhang C, Cai-yun F, Zhang L, Chen H, et al. Efficacy of Antifungal Drugs in the Treatment of Vulvovaginal Candidiasis: A Bayesian Network Meta-Analysis. Infect Drug Resist. 2018;Volume 11:1893–901.

Schwebke JR, Sobel R, Gersten J, Sussman SA, Lederman S, Jacobs M, et al. Ibrexafungerp Versus Placebo for Vulvovaginal Candidiasis Treatment: A Phase 3, Randomized, Controlled Superiority Trial (VANISH 303). Clinical Infectious Diseases. 2021;74(11):1979–85.

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