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A Multi-Target Symbiotic Formulation Reduces Recurrence in Recurrent Bacterial Vaginosis and Vulvovaginal Candidiasis: A Pilot Clinical Study

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Abstract

Background: Recurrent bacterial vaginosis (BV) and recurrent vulvovaginal candidiasis (RVVC) are highly prevalent conditions associated with substantial recurrence rates despite appropriate antimicrobial therapy. Dysbiosis of the vaginal microbiota is central to both disorders. Symbiotic formulations combining probiotics and prebiotics may enhance microbial restoration and reduce relapse. **Objective:** To evaluate recurrence rates, tolerability, and microbiome modifications in women with recurrent BV or RVVC treated with a novel oral symbiotic-based food supplement as adjunctive and prophylactic therapy. **Methods:** This was an interventional, uncontrolled pilot clinical trial enrolling reproductive-age women with recurrent BV or RVVC. After standard induction therapy (fluconazole or metronidazole), participants received a symbiotic supplement containing *Bifidobacterium breve* BR03, *Lactobacillus rhamnosus* LR04, N-acetylcysteine (NAC), fructooligosaccharides (FOS), pomegranate extract, zinc gluconate, and myrrh extract. The protocol included induction (10 days), prophylactic phase I (30 days), prophylactic phase II (60 days), and a 2-month follow-up. The primary outcome was recurrence rate. Secondary outcomes included Patients' Global Impression of Change (PGIC). **Results:** Twenty women were enrolled (11 with recurrent VVC and 9 with recurrent BV; mean age 37.7 years ± 11.0 years). During prophylaxis and follow-up, recurrence occurred in 6 patients (25%). Overall, 70% were classified as responders, 20% as partial responders, and 10% as non-responders. According to the PGIC scale, 70% of participants reported being "much improved" or "very much improved", and 65% expressed willingness to continue the supplement. The formulation was well tolerated; mild gastrointestinal discomfort occurred in 20% of patients and resolved spontaneously. **Conclusion:** The tested

symbiotic formulation showed potential in reducing recurrence of BV and RVVC and was well tolerated. Larger randomized controlled trials are warranted.

Keywords

Recurrent Vaginitis, Bacterial Vaginosis, Vulvovaginal Candidiasis, Symbiotic, Probiotics, Vaginal Microbiome

1. Introduction

Vaginal complaints, including abnormal discharge, malodor, pruritus, irritation, and burning, represent one of the most frequent reasons for gynecologic consultation, affecting more than 70% of adult women during their lifetime [1]. Bacterial vaginosis (BV) is a polymicrobial condition characterized by the disruption of lactobacilli-dominated vaginal microbiota and replacement by anaerobic species [2]. This condition arises from an imbalance in the vaginal microbiota and is associated with severe adverse health effects, including increased vulnerability to sexually transmitted infections (STIs), infertility, pelvic inflammatory disease, and complications during pregnancy. The prevailing treatment strategy for bacterial vaginosis often entails antibiotic therapy. Although metronidazole and clindamycin are effective short-term therapies, recurrence rates reach 50% - 60% within 1 - 3 months after treatment [1]. Vulvovaginal candidiasis (VVC) affects 70% - 75% of women at least once in their lifetime. Recurrent VVC (RVVC), defined as ≥3 - 4 episodes in 12 months, affects 10% - 15% of women [3]. While fluconazole maintenance regimens are effective, relapse occurs in approximately 60% within 6 months of discontinuation [4]. Given the central role of dysbiosis, probiotic therapy has been investigated to restore vaginal microbial balance. Probiotics comprising *L. crispatus*, *L. jensenii*, and *L. gasseri* have demonstrated efficacy in the treatment of BV [5].

A recent meta-analysis examined 17 randomized controlled trials (RCTs) encompassing a total of 3176 participants [6]. The results demonstrated that probiotics alone were markedly more beneficial than the placebo. Furthermore, probiotics administered alongside antibiotic therapy demonstrated greater efficacy than antibiotics alone (relative risk = 1.23, 95% CI: 1.05 - 1.43) in the management of BV. VVC is a common fungal infection that affects the vagina. It impacts around 75% of women at least once in their lifetime and is characterized by leukorrhea, severe pruritus, vulvar hyperemia, dysuria, and dyspareunia [3]. The prevailing treatment strategy generally encompasses antifungal therapy. *L. gasseri* and *L. crispatus* have demonstrated efficacy in suppressing the proliferation of *Candida albicans* [4]. A recent meta-analysis of 23 randomized controlled trials involving 2212 participants demonstrated that probiotics effectively prevent recurrent vaginal candidiasis at six months, with a pooled relative risk of 0.36, signifying that women utilizing probiotics were 64% less likely to experience a recurrence compared to

those not using probiotics [5]. The efficacy among various types of probiotics or formulations was identical. However, heterogeneity in strains, routes, dosage, and duration has limited definitive conclusions [7]. The present pilot study evaluates a novel oral symbiotic supplement combining *Bifidobacterium breve* BR03, *Lactobacillus rhamnosus* LR04, N-acetylcysteine (potential antibiofilm activity), fructooligosaccharides (prebiotic support), pomegranate extract, zinc gluconate, and myrrh extract (anti-inflammatory properties). The hypothesis is that this multitarget formulation may reduce recurrences of BV and VCC.

2. Methods

This interventional, uncontrolled, prospective pilot clinical trial enrolled women of reproductive age presenting with a diagnosis suggestive of BV or VVC and a documented history of recurrent vulvovaginal infections. Recurrent VVC and BV were defined as occurring in at least three to four confirmed episodes within the previous 12 months following the successful treatment of a prior episode [1] [3]. Pregnant women, women planning pregnancy during the study period, and postmenopausal women were excluded. Additional exclusion criteria included known hypersensitivity to any component of the investigational product, use of systemic or local antibiotics, antifungal agents, or probiotic preparations within the previous four weeks, presence of sexually transmitted infections, or genital dermatologic disorders. After verification of eligibility criteria and a detailed explanation of the study protocol, all participants provided informed consent. Baseline assessment included the collection of demographic and obstetric-gynecologic history, followed by a comprehensive vulvovaginal examination. For patients with suspected VVC, diagnosis was confirmed using the Sobel score (≥2), which evaluates pruritus, burning, erythema, and edema on a semi-quantitative scale ranging from 0 (absent) to 3 (severe), together with microscopic identification of blastospores or hyphae on fresh vaginal samples. BV was diagnosed according to Amsel criteria, requiring at least two of the following findings: homogeneous whitish or grayish discharge adhering to the vaginal walls, vaginal pH greater than 4.5, positive amine (whiff) test, and presence of clue cells on wet mount microscopy. All enrolled women underwent an induction phase consisting of standard pharmacological therapy according to diagnosis. Patients with VVC received oral fluconazole 200 mg administered on three alternate days during the first treatment week. Patients with BV were treated with intravaginal metronidazole gel once daily for five consecutive days. In addition to pharmacological therapy, all participants received the investigational oral food supplement during the induction phase at a dosage of two sachets per day for 10 days. The supplement manufactured by Cristalfarma-Italy contained in each sachet *Bifidobacterium breve* BR03 (3×10^9 CFU) and *Lactobacillus rhamnosus* LR04 (3×10^9 CFU) in combination with N-acetylcysteine (300 mg), fructooligosaccharides (100 mg), pomegranate extract (150 mg), zinc gluconate (7.5 mg), and myrrh extract (100 mg). At the end of the induction phase, patients were clinically reassessed. Only those considered clinically cured, defined as the absence of symptoms and negative microscopy, were eligible to en-

ter the prophylactic phase. During the first prophylactic phase, participants received one sachet of the supplement once daily for 30 consecutive days. Women who remained asymptomatic at the end of this period continued into a second prophylactic phase consisting of one sachet daily for an additional 60 days. Following completion of prophylactic therapy, participants entered a two-month observation phase without treatment. Clinical monitoring was performed throughout the study to detect recurrence. Recurrence was defined as the reappearance of clinical signs and symptoms accompanied by positive microscopy or culture findings. Based on clinical evolution, patients were classified as responders (absence of symptoms from baseline to final follow-up), partial responders (clinical relapse during follow-up), or non-responders (recurrence during the prophylactic phase).

Patient-reported treatment satisfaction and perceived improvement were assessed using the Italian version of the Patients' Global Impression of Change (PGIC) scale. Safety and tolerability were monitored throughout the study.

Data were analyzed using [statistical software, e.g., SPSS version 4.5, IBM Corp., Armonk, NY, USA/R software version 4.5.1]. Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), depending on data distribution assessed by the Shapiro-Wilk test. Categorical variables were reported as absolute numbers and percentages. The primary outcome was the recurrence rate of BV or VVC during the study period. Recurrence rates were calculated as proportions with 95% confidence intervals (CI). Comparisons between baseline and follow-up clinical parameters were performed using paired Student's t-test or Wilcoxon signed-rank test for continuous variables, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test.

A two-sided p-value < 0.05 was considered statistically significant. Given the exploratory nature of the study, no formal sample size calculation was performed. The trial was designed as a pilot study to generate preliminary efficacy and safety data.

3. Results

Study Population: A total of 37 women were screened, of whom 20 met the inclusion criteria and were enrolled in the study. 11 were diagnosed with recurrent VVC and 9 with recurrent BV. The mean age of participants was 37.7 years ± 11.0 years. Baseline demographic and clinical characteristics are summarized in **Table 1**.

Table 1. Baseline demographic and clinical characteristics.

Variable	Total (N = 20)
Age (years), mean ± SD	37.7 ± 11.0
BMI (kg/m^2), mean ± SD	23.0 ± 5.3
Recurrent VVC, n (%)	11 (55%)
Recurrent BV, n (%)	9 (45%)
Number of episodes in the previous 12 months, mean ± SD	7.2 ± 3.3

During the induction phase, clinical cure was achieved in all participants, so 20 patients entered the prophylactic phase.

During the prophylactic and follow-up periods, recurrence occurred in 6 patients (25%). Specifically:

- Responders (no recurrence throughout the study): 14 (%)
- Partial responders (relapse during follow-up): 4 (%)
- Non-responders (recurrence during prophylaxis): 2 (%)

Among women with recurrent VVC, the recurrence rate was 10%, while among women with recurrent BV it was 20% (**Table 2**, **Figure 1**). The overall recurrence rate observed during the study period was lower compared to historical recurrence rates reported in the literature (50% - 60% for BV and ~60% after fluconazole discontinuation in RVVC) [8].

Table 2. Clinical outcomes and recurrence rates.

Outcome	Total (N = 20)
Clinical cure after induction, n (%)*	20 (100%)
Responders, n (%)	14 (70%)
Partial responders, n (%)	4 (20%)
Non-responders, n (%)	2 (10%)
Overall recurrence rate, n (%)	6 (25%)
Recurrence rate in the RVVC subgroup	10%
Recurrence rate in the recurrent BV subgroup	20%
PGIC "much/very much improved", n (%)	14 (70%)

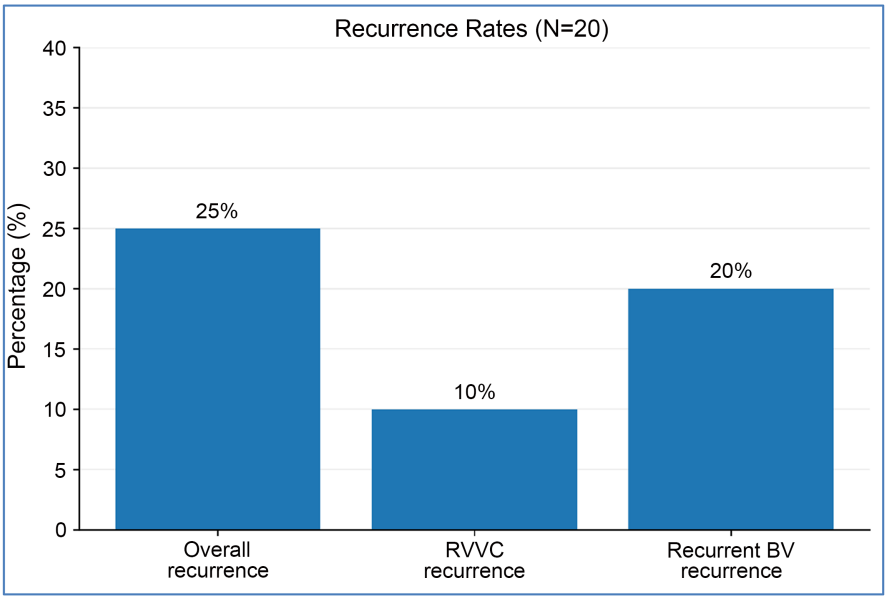

Figure 1. Recurrence rate.

According to the PGIC scale, 70% of participants reported "much improved" or "very much improved" symptoms at the end of the study period. Treatment satisfaction was high, with 65% of women expressing willingness to continue the supplement if recommended.

The investigational supplement was well-tolerated. Mild gastrointestinal discomfort was reported in 4 patients (20%), which resolved spontaneously. No serious adverse events were observed, and no participants discontinued treatment due to adverse effects.

4. Discussion

The recurrent BV and RVVC remain among the most therapeutically challenging conditions in gynecologic practice. Despite appropriate antimicrobial regimens, recurrence rates frequently exceed 50% within months, underscoring the limited ability of conventional therapies to restore durable vaginal eubiosis [8]. The present pilot study explored a multi-target symbiotic formulation designed not only to support microbial recolonization but also to interfere with biofilm persistence and inflammatory pathways. Our findings suggest a clinically meaningful reduction in recurrence rates compared with historical data following antimicrobial therapy alone. While cross-study comparisons must be interpreted cautiously, recurrence rates observed in our cohort were numerically lower than the 50% - 60% recurrence commonly reported for BV and the approximately 60% relapse rate after discontinuation of fluconazole prophylaxis in RVVC [9].

The rationale for combining probiotics, prebiotics, antibiofilm agents, and anti-inflammatory compounds reflects the multifactorial pathogenesis of recurrent vaginitis [10]. Persistent polymicrobial biofilms—particularly those involving Gardnerella vaginalis in BV and Candida spp. in RVVC—are increasingly recognized as key contributors to therapeutic failure [11]. N-acetylcysteine (NAC) has demonstrated mucolytic and antibiofilm properties, potentially facilitating disruption of structured microbial communities and enhancing probiotic recolonization [12]. The inclusion of *Lactobacillus rhamnosus* LR04 and *Bifidobacterium breve* BR03 was intended to promote restoration of a *Lactobacillus*-dominated microbiota and reinforce mucosal immune modulation. Although vaginal *Lactobacillus* species are classically dominant in healthy microbiota, oral administration may influence the vaginal ecosystem indirectly through gut-vaginal axis interactions, immune signaling pathways, and metabolic cross-talk [13]. The addition of fructooligosaccharides (FOS) may enhance probiotic survival and metabolic function. Botanical components such as pomegranate extract and myrrh, together with zinc, may contribute antioxidant and anti-inflammatory effects, potentially mitigating mucosal irritation and supporting epithelial barrier integrity [14] [15].

5. Conclusion

From a clinical perspective, the favorable tolerability profile observed in this study is noteworthy. No serious adverse events were reported, and adherence was high.

Given the chronic and relapsing nature of recurrent vaginitis, long-term safety and patient acceptability are critical determinants of therapeutic success. The absence of a control group precludes definitive causal inference, and the sample size was limited. Future randomized controlled trials with larger cohorts and extended follow-up are necessary to confirm efficacy, elucidate mechanisms, and determine cost-effectiveness. Despite these limitations, our results support the hypothesis that targeting multiple pathogenic mechanisms simultaneously, biofilm disruption, microbiota restoration, and inflammation modulation, may represent a promising paradigm shift in the management of recurrent vulvovaginal infections.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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