GOCM Gynecology and Obstetrics Clinical Medicine

Assessing the treatment effect of cranberry type A proanthocyanidins on vulvovaginal candidiasis: a randomised controlled clinical interventional study

Dongmei Wei [1,2] Yaoming Chen,[3] Yueyue Chen,[1,2] Tao Cui,[1,2] Xiaoyu Niu[1,2]

To cite: Wei D, Chen Y, Chen Y, *et al*. Assessing the treatment effect of cranberry type A proanthocyanidins on vulvovaginal candidiasis: a randomised controlled clinical interventional study. *Gynecology and Obstetrics Clinical Medicine* 2024;**4**:e000014. doi:10.1136/gocm-2024-000014

Received 22 February 2024
Accepted 19 April 2024

[1]Department of Gynecology and Obstetrics, West China Second Hospital, Sichuan University, Chengdu, China
[2]Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, China
[3]Chengdu Organic Chemistry Co., LTD, Chengdu, China

Correspondence to
Dr Xiaoyu Niu, Department of Gynecology and Obstetrics, Sichuan University West China Second University Hospital, Chengdu, Sichuan, China; hxfeynxy@126.com

ABSTRACT

Objective This study aimed to evaluate the efficacy and safety of cranberry extracts: A-type proanthocyanidins (A-PACs) in the treatment and prevention of vulvovaginal candidiasis (VVC).

Method An open, randomised, parallel-design study was conducted. A cohort of 300 eligible patients with VVC was recruited from the hospital. All participants were randomly divided into three groups according to a computer-generated randomisation list. Patients in group 1 were treated with standard antifungal therapy (oral single-dose fluconazole 150 mg and vaginal miconazole suppository 400 mg at bedtime for 3 days); patients in group 2 received oral A-PACs 16 mL two times per day for 6 days based on the treatment regimen of group 1; patients in group 3 were given oral A-PACs 16 mL two times per day for 6 days and vaginal miconazole suppository 400 mg at bedtime for 3 days. Patients who were clinically cured at the seventh day of follow-up in group 2 received maintenance therapy by oral A-PACs for 12 weeks.

Result At the seventh day of follow-up, the vaginal mycological results of all patients in group 2 who initially tested positive for pseudohyphae exhibited negative results. The negative conversion rates of fungal spores and blastospores in group 2 were superior to those in both group 1 and group 3. The symptoms of patients in group 2 ameliorated conspicuously compared with those in group 1 ($p<0.05$). The clinical cure rate of VVC in both group 2 and group 3 was not inferior to group 1. Cox regression analysis showed maintenance therapy was not significantly associated with short-term recurrence (HR 0.44 (0.11, 1.67); $p=0.23$) but could significantly diminish the risk of long-term recurrence (HR 0.57 (0.33, 0.99); $p<0.05$).

Conclusion This study revealed that A-PACs in cranberry juice combined with azole antibiotics can be used as a novel therapeutic option for the treatment and prevention of long-term recurrence of VVC.

Trial registration number ChiCTR2300076392.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Based on previous research, we observed that A-type proanthocyanidins (A-PACs), a component of American cranberry, exhibit anti-adhesive, encapsulating and expelling effects on certain pathogens in urinary tract infections, including *Candida albicans*, which is also a primary pathogen associated with vulvovaginal candidiasis (VVC). Currently, the mainstay of treatment for VVC is azole antifungals; however, they frequently entail safety and resistance concerns. Consequently, the exploration of alternative therapeutic modalities to conventional antifungal treatments is of escalating significance.

WHAT THIS STUDY ADDS

⇒ This clinical study has substantiated that A-PACs in cranberry juice combined with azole antibiotics are equally efficacious as the standard antibiotic regimen in the treatment of VVC. Furthermore, the oral administration of 8 mL Azmasol® for 12 weeks has demonstrated effectiveness in preventing long-term recurrence of VVC.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The clinical significance of this study offers additional therapeutic modalities for patients with VVC who may have contraindications to oral antifungal medication.

INTRODUCTION

Vulvovaginal candidiasis (VVC) is one of the most common vaginal infections worldwide, characterised by vaginal wall inflammation which is caused by *Candida* spp, especially *Candida albicans*, in the vaginal mucosa. The predominant species colonising the vagina are *C. albicans* and non-*albicans* species, such as *C. glabrata, C. tropicalis, C. krusei* and *C. parapsilosis*.[1] The former is the primary aetiological agent causing fungal inflammation. *Candida* spp are components of the vaginal flora in healthy women, of which opportunistic yeasts usually reside in the vaginal mucosa without causing any damage.[2] However, when there is an overgrowth of yeasts, and the cells invade the mucosa of the female genital tract, it transitions from a commensal organism to a pathogenic one, leading to the manifestation of infection signs

and symptoms,[3] consequently resulting in VVC. The most common symptoms of this condition include vulvovaginal itching, pain, burning, redness, and sometimes dysuria or dyspareunia, often accompanied by an abnormal vaginal discharge consisting of sloughed epithelium, immune cells, yeast and vaginal fluid.[4] Risk factors of VVC include antibiotic use, sexual activities, increased oestrogen levels (associated with high oestrogen oral contraceptives, pregnancy, hormone replacement therapies (HRTs), etc), uncontrolled diabetes mellitus, tight-fit clothing, humid weather and use of feminine hygiene products.[5] VVC is the most prevalent human candidal infection, posing a public health concern on a global scale. Approximately 75% of women experience at least one episode of VVC, and 40–45% experience it twice or more.[6] Moreover, recurrent VVC (RVVC), defined as four or more confirmed infections within 1 year, affects up to 10% of women.[7] The incidence of VVC notably elevates among women of childbearing age as opposed to those in the prepubertal or postmenopausal phases.[8] This augmented susceptibility to *C. albicans* infection primarily emanates from high oestrogen levels, induced either by HRT or pregnancy.

VVC is commonly diagnosed through clinical examination, vaginal secretion microscopy and mycological culture. The identification of colonies on mycological culture media is considered the 'golden standard' in diagnosis. Concurrently, biochemical or molecular assays provide an alternative approach to detect VVC, with research supporting their superior diagnostic performance over clinical microscopic examination.[9 10] The mainstay of treatment for uncomplicated VVC is azole antifungals, which act by inhibiting the fungal enzyme CYP51 and preventing the accumulation of fungi toxic sterols.[11] Imidazoles (miconazole nitrate, fenticonazole, econazole, clotrimazole) and triazoles (fluconazole, itraconazole and voriconazole) are typical components of azole antifungal drug therapy. These medications are available in various formulations for oral or local administration, including vaginal creams, ointments or suppositories. Additional conventional treatment options encompass polyenes (amphotericin B, nystatin) and ciclopiroxolamine, acting on altering the permeability of the fungal wall and inhibiting important iron-dependent enzymes, respectively.[12 13] Nystatin is considered to be less efficacious than azole agents, and reports of treatment failures are common. Given that oral administration of drugs typically poses a higher risk of severe systemic side effects compared with topical application, the 2021 Centers for Disease Control and Prevention guidelines recommend the effective management of uncomplicated VVC with short-course topical formulations (ie, single dose and regimens of 1–3 days). Treatment with azoles results in relief of symptoms and negative cultures in 80–90% of patients who complete therapy.[6] For RVVC, oral fluconazole emerges as the first option for maintenance treatment in all guidelines. Secondary maintenance therapies include oral itraconazole or topical clotrimazole.[14]

Fluconazole is the primary treatment for RVVC and has been substantiated to enhance the quality of life in 96% of women.[15] Nevertheless, achieving a complete cure remains challenging. A study suggested that the proportion of women without relapse at 6, 9 and 12 months after the initial maintenance fluconazole course was 90.8%, 73.2% and 42.9%, respectively.[16] Therefore, long-term antifungal prophylaxis is often necessary through maintenance regimens. However, excessive exposure to such maintenance protocols and regular use of over-the-counter or prescription therapies may augment the potential of developing fluconazole-resistant strains. All women diagnosed with resistant *C. albicans* strains have a history of fluconazole exposure.[17] Furthermore, topical antifungal medications may lead to side effects such as itching and a burning sensation,[18] while oral administration may result in headaches and gastrointestinal disorders.[1] Additionally, patients may face the risk of drug interactions with other medications. Fluconazole is associated with adverse effects, encompassing hepatotoxicity, cytochrome P450 interactions and possible fetal harm in pregnant women such as spontaneous abortion and congenital anomalies.[6] In general, current azole antifungal treatments are commonly related to safety and resistance issues. Alternative therapeutic strategies to conventional antifungal treatments are becoming increasingly crucial.

Some research shows that cranberry extract exhibits anti-adhesive activity against *C. albicans*, serving as a non-resistant food ingredient. This characteristic positions it as an auxiliary therapy for the treatment and long-term prevention of RVVC or VVC.[19] A-PACs refer to A-type proanthocyanidins, with American cranberries predominantly containing proanthocyanidins of the A-type structure. Available clinical studies show that cranberry juice is effective in preventing recurrent urinary tract infections.[20] The minimal concentration of A-PACs in cranberry juice required for anti-adhesive activity against pathogens was 60 µg/mL.[21] An effective dose of A-PACs at 36 mg administered two times per day, with a 12-hour interval, demonstrated efficacy in human trials.[22] In the context of urinary tract infections, cranberry juice has been endorsed in several recent clinical guidelines for the management and prevention of infections among adolescents, women during pregnancy, and patients with severe hepatic or renal impairment.[23–25] Considering the safety, accessibility and non-resistance of cranberry juice, we formulated a clinical trial to probe into the efficacy and safety of A-PACs in the management and prevention of VVC. The selected dosage aligns with the effectiveness observed in preceding clinical trials.[19]

METHOD

Study design and patients

This clinical interventional study was an open, randomised, parallel-design study conducted at West China Second Hospital of Sichuan University from March 2021 to April 2022.

The diagnosis of VVC was established in a woman exhibiting symptoms when a wet smear of vaginal discharge, treated with either 10% potassium hydroxide or saline, demonstrated the presence of spores, blastospores or pseudohyphae. Alternatively, a positive result for a yeast species was obtained from a culture.[6] The study enrolled female participants aged 18–60 years, who were generally in good health and presented with VVC. Inclusion criteria stipulated that individuals had not received antibiotics or cranberry extract within the preceding 2 weeks. Patients were excluded from the trial if they met any of the following criteria: (1) exhibited hypersensitivity to antibiotics or cranberries; (2) were either pregnant or actively attempting conception; (3) possessed a medical history involving kidney transplantation, kidney stones or kidney tumours. Considering an 84% cure rate for patients who were treated with standard antifungal therapy,[26] a non-inferiority margin of −10%,[27] a power of 90% and a significance level of 5%, the sample size was calculated as 80 participants per group, then increased to 100 to take into account a dropout rate of 20% in each group. Hence, a cohort of 300 patients from the Obstetrics and Gynecology Clinic of West China Second Hospital of Sichuan University was incorporated into this study. The calculation formula was as follows:

Two sides:

$$n_T\left[\frac{Z_{1-\alpha/2}\times\sqrt{p(1-p)(1+k)/k}+Z_{1-\beta}\times\sqrt{p_T(1-p_T)+p_C(1-p_C)/k}}{p_T-p_C}\right]^2$$

$$n_C = K\times n_T$$

Note:

$$p = \left(p_T + K\times p_C\right) / \left(K+1\right)$$

Treatment regimens

The investigational product, Azmasol® (UPWELL, Canada), contains 36 mg of A-PACs per 8 mL, which consists of 15–18% A-type PACs, as assayed by the Brunswick Laboratories 4-dimethylaminocinnamaldehyde, the method now endorsed by the US Department of Agriculture, the Cranberry Institute and Rutgers University.[21 22]

The purpose of this study was to investigate the efficacy and safety of A-type PACs at this concentration in the treatment of patients with VVC.[19] According to the computer-generated randomisation list, all patients were randomly assigned into three groups (group 1, group 2 and group 3) with a 1:1:1 allocation. Patients in group 1 were treated with standard antifungal therapy (oral single-dose fluconazole 150 mg and vaginal miconazole suppository 400 mg at bedtime for 3 days); patients in group 2 received oral A-type PACs 16 mL two times per day for 6 days based on the treatment regimen of group 1; patients in group 3 were given oral A-type PACs 16 mL two times per day for 6 days and vaginal miconazole suppository 400 mg at bedtime for 3 days. Following the exclusion of 31 patients lost to follow-up, treatment outcomes for 269 patients were collected on the seventh day of follow-up.

Additionally, this investigation extended to explore the potential of A-type PACs in preventing the recurrence of VVC. Patients who were clinically cured at the seventh day of follow-up and willing to prolong their participation were monitored for recurrence of VVC. Due to the limited and inconsistent proportion of patients with RVVC in each group, they were not included in the subsequent study. Given our dual objective of assessing both the short-term efficacy and safety of A-type PACs treatment in VVC, alongside observing its long-term effectiveness and safety, and considering the consistency of antifungal treatment drugs in groups 1 and 2 as opposed to the disparity in group 3, we opted for group 2 as the cohort for A-type PACs long-term intervention in VVC. Ultimately, the second phase of this study delineated a refined cohort, segregating the participants clinically cured at the seventh day of follow-up into two distinct groups. The A-type PACs maintenance intervention group encompassed 71 patients from the original group 2 without recurrence, while the non-intervention group consisted of 135 patients from the original group 1 (57 patients) and group 3 (78 patients) with recurrence-free.

Study procedures

At the study's commencement, the patients completed the general condition questionnaire, the leucorrhoea examination and the symptom assessment. The presence of fungus, specifically spores, pseudohyphae and blastospores, was determined based on the leucorrhoea examination results. Clinical symptom assessment of VVC encompassed the comprehensive aggregation of respective symptom scores. Each symptom and sign, including burning, itching, discharge and erythema, received a numerical score as follows: 0 (absent), 1 (mild), 2 (moderate) or 3 (severe).[28] The symptom score was a composite score (global score) comprising the sum of all individual scores, used to evaluate the effect of treatment on the global symptomatology and manifestations of VVC (score range 0–9). The severity of VVC was gauged using the composite score (maximum of 9), with a score of 7 or higher indicating severe VVC. The symptoms evaluated were self-reported by the participants.

The patients were followed up on the seventh day after the initial oral dose to assess the therapeutic efficacy. Subsequently, the leucorrhoea examination and symptom assessment were performed again. The clinical cure was ascertained by the physician based on the patient's overall condition. Those clinically cured at the seventh day of follow-up underwent ongoing surveillance for recurrence of VVC within a period, with short-term and long-term endpoints set at 4 weeks and 12 weeks, respectively. The determination of participant relapse was also made by the clinician, and the time of recurrence or censoring was recorded. The study flow chart is illustrated in figure 1.

Clinical cure was defined as the conversion to negative fungal assay findings for pseudohyphae, spores and blastospores in vaginal discharge examination at the seventh day of follow-up, accompanied by symptom alleviation (ie,

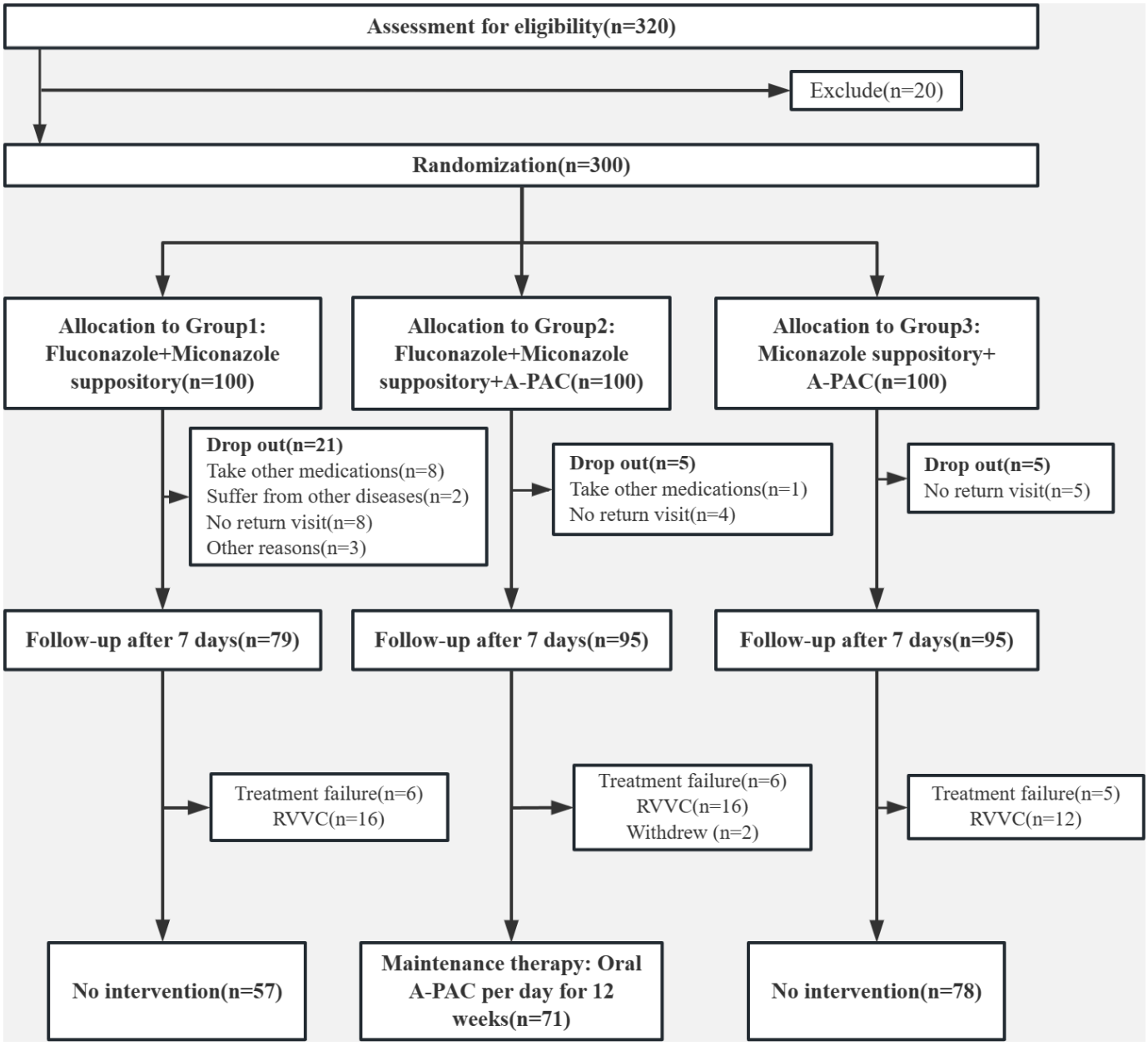

Figure 1 Flow chart of the study. RVVC represents patients with a history of RVVC before inclusion. Treatment failure is defined as patients who were not clinically cured at the seventh day of follow-up. RVVC, recurrent vulvovaginal candidiasis.

absence of itching symptoms). The clinical cure rate and disease-free survival were the primary outcomes in our study, the secondary outcomes included microbial clearance rates and composite symptom score. Following the exclusion of patients not clinically cured at the seventh day of follow-up, comparability among the remaining cohorts was compromised due to divergent baseline characteristics.

Statistical analysis

Categorical data were presented by number (percentages) and compared by X^2 or Fisher's exact test. Continuous data were expressed as mean (SD) for normally distributed data or median (P_{25}~P_{75}) for skewed data, and compared by Student's t-test or non-parametric test. This study aimed to demonstrate the non-inferiority of clinical cure rate in group 2 and group 3, with a hypothesis of a non-inferiority margin of −10%. Disease-free survival for short-term and long-term recurrence was calculated using the Kaplan-Meier method, and the log-rank (Mantel-Cox) analysis gauged statistical differences. Considering the absence of randomisation and the dissimilarity between the two groups, potential confounding factors influencing the risk of recurrence were adjusted. Then, multivariable Cox proportional hazards models were applied to analyse the disparity in disease-free survival between the maintenance therapy group and the non-intervention group, aiming to assess the

potential of cranberry juice in preventing the recurrence of VVC. HRs and 95% CIs depicted these results. The statistical significance was set at p<0.05, and all statistical analyses were performed by using R V.4.0.3.

RESULT

Baseline characteristics

A total of 269 patients with VVC were enrolled in the study. The average ages of participants were 34.7 (±8.5) years old in group 1, 33.7 (±6.3) years old in group 2 and 35.3 (±8.9) years old in group 3, respectively. Monthly family income was divided into three categories: low (<5000 renminbi (RMB)), middle (5000~10 000 RMB) and high (>10 000 RMB).[29] A significant difference was found in monthly family income (p<0.05). There was no significant difference in age, marital status, education years or history of childbearing for the three groups (p>0.05). In total, 44 patients experienced four or more VVC episodes in the past year, with the number of RVVCs being 16 (20.3%), 16 (16.8%) and 12 (12.6%) in group 1, group 2 and group 3, respectively. No significant differences were observed. The baseline demographic characteristics of the three groups are shown in table 1.

Table 1 Baseline demographic characteristics of study groups

Characteristics	Group 1 (N=79)	Group 2 (N=95)	Group 3 (N=95)	P value
Age in years (mean±SD)	34.7±8.5	33.7±6.3	35.3±8.9	0.36
Marital status				0.71
Married	18 (22.8)	24 (25.3)	17 (17.9)	
Single	56 (70.9)	67 (70.5)	74 (77.9)	
Separated (divorced or widowed)	5 (6.3)	4 (4.2)	4 (4.2)	
Education years				0.09
≤9	22 (27.8)	11 (11.6)	16 (16.8)	
9~12	26 (32.9)	37 (38.9)	37 (38.9)	
>12	31 (39.2)	47 (49.5)	42 (44.2)	
Monthly family income				<0.05
Low	32 (40.5)	21 (22.1)	34 (35.8)	
Middle	32 (40.5)	33 (34.7)	28 (29.5)	
High	15 (19.0)	41 (43.2)	33 (34.7)	
History of childbearing				0.63
Yes	55 (69.6)	70 (73.7)	64 (67.4)	
No	24 (30.4)	25 (26.3)	31 (32.6)	
RVVC				0.39
Yes	16 (20.3)	16 (16.8)	12 (12.6)	
No	63 (79.7)	79 (83.2)	83 (87.4)	
Wiping direction after defecation				0.20
Urethra–vagina–anus direction	48 (60.8)	70 (73.7)	65 (68.4)	
Anus–vagina–urethra direction	31 (39.2)	25 (26.3)	30 (31.6)	
Change underpants every day				0.25
Yes	74 (93.7)	87 (91.6)	82 (86.3)	
No	5 (6.3)	8 (8.4)	13 (13.7)	
Frequency of sexual activity				0.60
No	18 (22.8)	28 (29.5)	20 (21.1)	
1~5 times a month	50 (63.3)	55 (57.9)	66 (69.5)	
More than 5 times a month	11 (13.9)	12 (12.6)	9 (9.4)	
Oral contraceptives				0.43
Yes	8 (10.1)	9 (9.5)	4 (4.2)	
No	71 (89.9)	86 (90.5)	91 (95.8)	

Values are mean±SD, n (%) or median (P_{25}~P_{75}).
RVVC, recurrent vulvovaginal candidiasis.

Table 2 The clinical cure rates and clearance rates of three groups at seventh day of follow-up

Parameters	Group 1	Group 2	Group 3	Difference (95% CI), p value	
				Group 1 vs 2	Group 1 vs 3
Clinical cure, n (%)					
All	72/79 (91.1)	89/95 (93.7)	88/95 (92.6)	2.6 (–6.6, 11.7), <0.01	1.5 (–7.8, 10.8), <0.01
no RVVC	57/63 (90.5)	73/79 (92.4)	78/83 (94.0)	0.9 (–8.8, 12.7), <0.01	3.5 (–6.8, 13.8), <0.01
RVVC	15/16 (93.8)	16/16 (100.0)	10/12 (83.3)	–	–
Clearance rate, n (%)					
Spore	62/70 (88.6)	83/90 (92.2)	82/91 (90.1)	3.6 (–6.9, 14.2), 0.61	1.5 (–9.4, 12.5), 0.96
Pseudohyphae	36/39 (92.3)	54/54 (100.0)	37/40 (92.5)	7.7 (–2.9, 18.3), 0.07	0.2 (–11.7, 12.1), 0.99
Blastospore	63/70 (90.0)	85/91 (93.4)	84/91 (92.3)	3.4 (–6.5, 13.4), 0.62	2.3 (–7.9, 12.5), 0.82

The non-inferiority of the proportion with clinical cure was evaluated as a primary outcome, with a hypothesis of a non-inferiority margin of –10%.
The clearance rates were compared by X^2 or Fisher's exact test.
In the clearance rate analysis, only participants with positive results in baseline mycological testing for each indicator were included, totalling 251 participants for spores (70, 90, 91 in groups 1, 2 and 3), 133 for pseudohyphae (39, 54, 40 in groups 1, 2 and 3) and 252 for blastospores (70, 91, 91 in groups 1, 2 and 3).
RVVC, recurrent vulvovaginal candidiasis.

Therapeutic effect

According to follow-up after 7 days, the clinical cure rates from group 1 to group 3 were 91.1% (72 of 79), 93.7% (89 of 95) and 92.6% (88 of 95), respectively. Based on the non-inferiority margin value of 10%, patients in both group 2 and group 3 demonstrated therapeutic effects not inferior to those in group 1 (table 2). Among the 44 patients with RVVC, 3 remained clinically uncured, with 1 case in group 1 and 2 cases in group 3. Due to the limited sample size, statistical analysis was omitted. Excluding patients with RVVC, the clinical cure rates in the remaining patients were 90.5% (57 of 63) in group 1, 92.4% (73 of 79) in group 2 and 94.0% (78 of 83) in group 3. Compared with group 1, the hypothesis of non-inferiority of the clinical cure rate in group 2 and group 3 was established successfully.

After the loss of 10 participants during follow-up (including 5 cases from group 1, 2 cases from group 2 and 3 cases from group 3), a total of 259 patients completed mycological testing at both baseline and the seventh day of follow-up. Clearance rates for the three indicators (spore, pseudohyphae and blastospore) were individually calculated on the seventh day of follow-up. All patients in group 2 demonstrated complete clearance of initially positive fungal pseudohyphae in their vaginal secretions, with a negative conversion rate of 100%, surpassing the rates observed in group 1 (92.3%) and group 3 (92.5%). Regarding fungal spore, patients in group 1, group 2 and group 3 exhibited a negative conversion rate of 88.6%, 92.2% and 90.1%, respectively. For fungal blastospore, conversion rates to negative were 90.0%, 93.4% and 92.3% for group 1, group 2 and group 3 patients, respectively. Notably, the negative conversion rates of fungal spores and blastospores in group 2 were superior to those in both group 1 and group 3. However, in comparison with group 1, there was no significant difference in the clearance rate of spore, pseudohyphae and blastospore for group 2 or group 3, for all calculated p values exceeded 0.05 (table 2).

A total of 260 patients had completed symptom assessment, with 9 participants (including 4 cases from group 1 and 5 cases from group 2) having no symptom scores due to the loss of follow-up. The symptom scores averagely decreased by 1.0 (5.3×10^{-5}, 2.0) in group 2 than in group 1 ($p<0.05$), but there was no statistically significant difference between group 1 and group 3 ($p=0.43$) (table 3). In conclusion, about treatment outcomes, patients in group 2 (receiving a combination of oral fluconazole and vaginal miconazole suppository with A-type PACs) exhibited superior improvement in symptoms compared with those in group 1 (treated with only oral fluconazole and vaginal miconazole suppository). Group 3, subjected to A-type PACs combined with vaginal miconazole suppository treatment, demonstrated efficacy comparable with the therapeutic regimen implemented in group 1.

Short-term recurrence

After completing treatment, 206 subjects were followed for recurrence of VVC. At the 4-week follow-up, 11 (8.1%) patients in the non-intervention group relapsed, while only 3 (4.2%) patients in the maintenance therapy

Table 3 The composite symptom scores of three groups at baseline and seventh day

Parameters	Group 1	Group 2	Group 3	Difference (95% CI), p value	
				Group 1 vs 2	Group 1 vs 3
Symptom score at baseline	4.0 (3.0, 6.0)	5.0 (3.3, 7.0)	4.0 (3.0, 5.0)	−1.0 (−1.0, 0.0), 0.05	5.5×10^{-5} (-2.9×10^{-5}, 1.0), 0.67
Symptom score at seventh day	2.0 (2.0, 4.0)	2.0 (1.0, 3.8)	2.0 (1.0, 3.0)	5.3×10^{-5} (-2.4×10^{-5}, 1.0), 0.19	7.3×10^{-6} (-2.9×10^{-5}, 1.0), 0.28
Change in score	−1.0 (−3.0, 0)	−2.0 (−4.8, 1.0)	−2.0 (−3.0, −0.5)	1.0 (5.3×10^{-5}, 2.0), 0.01	1.0 (-4.1×10^{-5}, 1.0), 0.43

The symptom scores were compared by the Wilcoxon rank-sum test.

group did (p=0.39). Meanwhile, when accounting for both the incidence and timing of recurrence, there was no substantial difference in disease-free survival between the two groups, as manifested by the Kaplan-Meier survival analysis (figure 2, p=0.28). The Cox regression analysis also revealed that maintenance therapy was also not significantly associated with short-term disease-free survival (table 4; HR 0.44 (0.11, 1.67); p=0.23).

Long-term recurrence

At the 12-week follow-up, 52 (38.5%) out of 135 patients in the non-intervention group experienced a recurrence, whereas 19 (26.8%) out of 71 patients in the maintenance therapy group relapsed (p=0.13). Considering both recurrence incidence and its timing, Kaplan-Meier survival analysis showed that there was no significant difference in disease-free survival (figure 3, p=0.06). Nevertheless, in the multivariable analysis, maintenance therapy could significantly diminish the risk of long-term recurrence (table 4; HR 0.57 (0.33, 0.99); p<0.05).

DISCUSSION

In this randomised, group-controlled interventional study, A-PAC in cranberry juice exhibited efficacy comparable with the azole antibiotics recommended in the guidelines for treating VVC. Our findings suggested that A-PAC in cranberry juice combined with azole antibiotics can be used as an alternative therapy for the treatment and prevention of VVC. Despite the established effectiveness of traditional antifungal drugs in VVC treatment, the escalating antibiotic resistance poses a challenge.[6] Our study proposed a novel solution to this predicament. Studies have shown that *C. albicans* is essentially a polymorphic fungus. Its mycelial stage demonstrates heightened invasiveness, correlating with an increased likelihood of infection and clinical manifestations.[30] Previous research has substantiated that A-PACs significantly reduced the adhesion of *C. albicans* to oral mucosal epithelial cells.[19] Our work hypothesises that the unique anti-adhesion structure of A-PACs in cranberry juice may physically encapsulate mycelium, thus impeding the fungus from infecting human cells. This mechanism of action in this regard can be further investigated in future research. Our clinical interventional study further confirmed its anti-adhesive efficacy within the female vagina. When combing cranberry juice with antibiotics for treatment (group 2), the clearance rate of pseudohyphae even reached 100%, accompanied by a substantial improvement in clinical symptoms. Besides, although the sample size was small, all patients with RVVC in group 2 were clinically cured. This experiment demonstrates that cranberry juice in combination with azole antibiotics administered orally

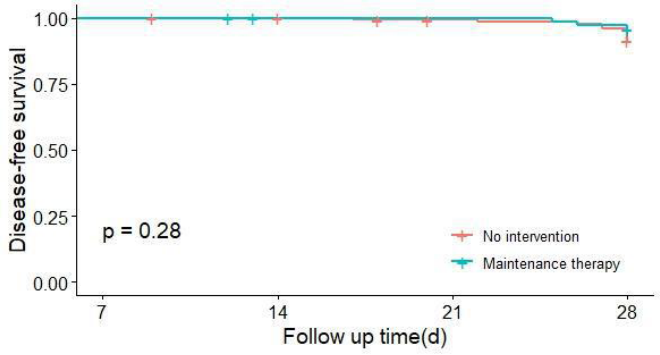

Figure 2 The Kaplan-Meier curves of disease-free survival in the maintenance therapy group and no intervention group at 4-week follow-up.

Table 4 The results of the multivariable Cox regression analysis at 4-week and 12-week follow-up

	HR	95% CI	P value
Model 1: short term (4 weeks)			
Maintenance therapy	0.44	0.11, 1.67	0.23
Model 2: long term (12 weeks)			
Maintenance therapy	0.57	0.33, 0.99	<0.05

Each model was adjusted for age, monthly family income, education years, frequency of sexual activity, oral contraceptives (yes or no), history of childbearing (yes or no), wrong wiping direction after defecation (wiping from the anus–vagina–urethra direction), change underpants every day (yes or no).

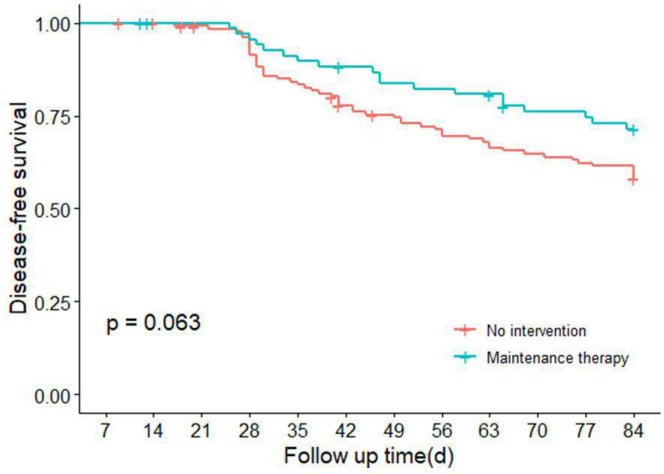

Figure 3 The Kaplan-Meier curves of disease-free survival in the maintenance intervention group and non-intervention group at 12-week follow-up.

and topically exhibits both therapeutic and preventive effects against the long-term recurrence of VVC. Notably, this represents the inaugural investigation showcasing cranberry juice as an effective treatment for VVC. The results of this trial hold substantial practical significance for individuals unable to tolerate oral antibiotics (eg, those preparing for conception, pregnant women and those with impaired liver function), providing them with a valuable new option.

A questionnaire study involving 65 adult women[31] showed that consumption of cranberry juice was associated with a risk of VVC. Commercially available cranberry juice often contained a lot of added sugar to improve its taste, which, in itself, was also a risk factor for VVC.[32] However, the mentioned study did not compare the composition of different cranberry juices. The cranberry juice used in this research had no added sugar and significantly higher levels of A-PACs as opposed to regular cranberry juice (the proanthocyanidin content of fresh American cranberries is approximately 34.3 mg/100 g, with 51–91% being A-PACs).[33] This study revealed that cranberry juice containing high A-PACs content combined with azole antibiotics was as effective as the guideline-recommended standard antifungal therapy in the treatment of VVC. Future studies involving larger cohorts of women with VVC are warranted.

While key findings indicated that the effect of A-PACs did not attain statistical significance at the 4-week follow-up due to small sample sizes, it was significant at the 12-week follow-up. Establishing a robust vaginal ecosystem is essential to mitigate the risk of recurrence and resist *Candida* strains.[34] Thus, maintenance therapy plays a crucial role in preventing vaginal recolonisation. Cranberry juice, as a 'natural antibiotic', could serve as a preventive strategy for individuals with compromised health, particularly pregnant women and children who may not be well suited to antibiotics.

This study has certain limitations that should be acknowledged. First, the sample size was restricted, and dropouts during the follow-up were not uncommon, especially for group 1. Second, the latter part of the experiment deviated slightly from strict randomisation. Clinically cured patients in the original group 2 at the seventh day of follow-up underwent maintenance therapy, whereas those in the remaining two groups, without recurrence at the seventh day of follow-up, received no intervention. This introduced a subjective bias into the study. Moreover, forthcoming randomised controlled trials are imperative to assess the preventive effect of A-PACs in cranberry juice against recurrence. Patients with RVVC were excluded from the analysis of VVC recurrence due to their limited numbers and uneven distribution across groups. As the prevalence of patients with RVVC increases, further analyses can be undertaken to investigate the presence of a preventive effect for these individuals. Third, it is crucial to highlight that this was a single-centre, open-label trial, and therefore, the placebo effect cannot be disregarded. Future research should validate our results through multicentre, double-blind and large-sample studies.

CONCLUSION

Our clinical interventional study has substantiated that A-PACs in cranberry juice combined with azole antibiotics are equally efficacious as the standard antibiotic regimen in the treatment of VVC. Furthermore, the oral administration of 8 mL A-PACs for 12 weeks has demonstrated effectiveness in preventing long-term recurrence of VVC.

Contributors DW is responsible for conceptualisation, methodology, formal analysis, investigation, writing (original draft) and the overall content as guarantor. YaC is responsible for formal analysis, data collection, and investigation and supervision. YuC is responsible for conceptualisation, methodology, writing (review and editing) and supervision. TC is responsible for data collection, supervision and methodology. XN is responsible for conceptualisation, methodology, writing and editing, supervision and project administration. All authors agree to publish this article.

Funding This study was supported by the Foundation of Sichuan University (no. 21H0103), Science & Technology Department of Sichuan Province (no. 2019YFS0008), the National Key Research and Development Program of China (no. 2021YFC2009100), Health Commission of Sichuan Province (no. 21ZD002), Research Projects of Sichuan Science and Technology Department (no. 2023YFQ0070), and Key Research Projects of Sichuan Science and Technology Department (no. 2023YFG0128, no. 2023NSFSC1606, no. 23ZDYF2049).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Ethical approval was granted by the the Ethics Committee of West China Second Hospital of Sichuan University (No. 2021146) on March 1, 2021. Informed consent was obtained from all participants. All procedures were performed in accordance with relevant guidelines.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request by the corresponding author.

ORCID iD

Dongmei Wei http://orcid.org/0000-0001-6922-0296

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