https://doi.org/10.31925/farmacia.2019.6.1 **REVIEW**

HERBAL MEDICINES AGAINST BACTERIAL VAGINOSIS IN WOMEN OF REPRODUCTIVE AGE: A SYSTEMATIC REVIEW

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Abstract

The aim of this systematic review was to present the effect of herbal medicines on both clinical symptoms and laboratory findings of bacterial vaginosis in the reproductive age. Four major databases (PubMed, Scopus, ISI Web of Science, and Cochrane Library) were systematically searched for articles that evaluated the effect of herbal medicines on bacterial vaginosis and were published until July 31, 2019. *Zataria multiflora* was found to be as effective as oral or vaginal metronidazole in improvement of both clinical symptoms and laboratory parameters. However, it caused vaginal irritation and burning. The effect of garlic tablet was reported to be more marked than oral metronidazole in alleviating the clinical symptoms and comparable to that of oral metronidazole in improving laboratory findings. The effect of *Nigella sativa* was similar to metronidazole in treating both clinical symptoms and laboratory findings. *Hypericum perforatum* vaginal gel 3% has proved to be as effective as metronidazole vaginal gel 0.75% in preventing bacterial vaginosis. Cure rate (recovery) in *Myrtus communis* L. plus metronidazole or *Berberis vulgaris* plus metronidazole was higher than that of metronidazole alone. Treatment with *Hypercum perforatum* for a week was very well tolerated, and caused no side effect. Herbal medicines including *H. perforatum, Z. multiflora, B. vulgaris* and *Allium sativum* was found to be as effective as metronidazole with a fewer side effect. Hence, they might be considered potential candidates to combat vaginosis.

Rezumat

Scopul acestui *review* a fost de a prezenta efectul produselor din plante atât asupra simptomelor clinice, cât și a rezultatelor de laborator în vaginoza bacteriană, la vârsta reproducerii. Patru baze de date majore (PubMed, Scopus, ISI Web of Science și Biblioteca Cochrane) au fost consultate sistematic privind studii care au evaluat efectul derivatelor din plante asupra vaginozei bacteriene și publicate până la 31 iulie 2019. *Zataria multiflora* s-a dovedit la fel de eficientă, pe cale orală sau vaginală, ca și metronidazolul în îmbunătățirea simptomelor clinice și a parametrilor de laborator. Cu toate acestea, a provocat iritații și arsuri vaginale. Efectul extractelor de usturoi, administrate oral, a fost raportat a fi mai superior metronidazolului administrat oral. Efectul extractului de *Nigella sativa* a fost similar cu metronidazolul în tratarea atât a simptomelor clinice, cât și în normalizarea datelor de laborator de laborator. *Hypericum perforatum* gel vaginal 3% s-a dovedit a fi la fel de eficient ca metronidazolul vaginal 0,75%. Efectul asocierii extractelor de *Myrtus communis* L. sau *Berberis vulgaris* și metronidazol a fost mai superior comparativ cu metronidazolul administrat singur. Tratamentul cu *Hypercum perforatum* timp de o săptămână a fost foarte bine tolerat și nu a avut efecte secundare. Produsele din plante, inclusiv *H. perforatum, Z. multiflora, B. vulgaris* și *Allium sativum* s-au dovedit a fi cel puțin la fel de eficiente ca și metronidazolul, cu un efecte secundare mai puține.

Keywords: bacterial vaginosis, *Gardnerella vaginalis*, herbal medicine, medicinal plants, *H. perforatum, Z. multiflora, B. vulgaris, Allium sativum, Nigella sativa*

Introduction

Urogenital infections including urinary tract infections and yeast vaginitis affect the quality of life of the patients and impose a considerable burden on the healthcare system [1]. Approximately two-third of female's experience vaginitis at least once during their lifetime. It was reported that 90% of vaginitis cases

are secondary to infections like bacterial vaginosis (BV), vaginal candidiasis, and *Trichomonas vaginalis* [2]. Bacterial vaginosis is associated with alteration of vaginal flora leading to a decrease in normal *lacto-bacillus* microflora and an increase in anaerobic bacteria, *Gardnerella vaginalis*, and *Mycoplasma hominis*. This infection may occur frequently in women of reproductive age. One of the BV clinical manifestations is vaginal discharge, mostly with a fishy odour, that is exacerbated usually after sexual intercourse [3]. The global prevalence of BV was estimated to vary between 22% and 50% with 20 - 49% in Africa, 11% in the UK and 15 - 30% in the USA [4], as it is more prevalent in developing countries [3]. BV is the most frequent cause of vaginal discharge, observed in 22% to 50% of cases, and half of the infected women are asymptomatic [5]. BV can cause preterm labour, pelvic inflammatory disease and sexually transmitted diseases (STD) like human immune deficiency virus (AIDS) [1, 6, 7].

Common antibiotics including clindamycin, metronidazole and tinidazole are wildly used for treatment of BV. But recurrence often occurs following the primary response to therapy [8].

Complications caused by chemical drugs have encouraged both patients and researchers to examine the efficacy and safety of probiotics [9, 10] or herbal medicines against various diseases including BV [11]. To the best of our knowledge, there is no systematic review presenting the effect of herbal medicines on BV. The present article reviews the herbal medicines that were shown to be effective on both clinical symptoms and laboratory findings in women of reproductive age who were diagnosed with BV.

Materials and Methods

The process of trials selection is shown in Figure 1. Main demographic and clinical characteristics of the patients as well as the methodologies of the trials included in the systematic review are shown in Table II.

Search strategy

Four major databases, PubMed, Scopus, Cochrane Library, and Web of Science, were checked during screening. The above-noted databases were systematically searched for studies that examined possible effects of herbal medicines on BV in females of reproductive age and were published until July 31, 2019. For this purpose, we used the following search string: ((bacterial vaginosis) OR (bacterial vaginitis) OR (bacterial vaginoses)) AND ((herbal medicine) OR (plant extract*) OR (medicinal plant*) OR (herb) OR (botany) OR (pharmacognosy) OR (phytotherapy) OR (naturopathy) OR (plant* medicinal) OR (herbal drug*) OR (herbal remedy) OR (herbal preparation*) OR (herbal product*) OR (herbal supplement*) OR (traditional medicine) OR (complementary medicine) OR (alternative medicine)). Two reviewers independently screened all abstracts and full-text articles. Any discrepancies were resolved by discussion, and where no agreement was reached, an independent third-party was involved.

Inclusion criteria

All clinical trials were included in this systematic review if herbal medicines were orally or vaginally administrated as mono-therapy or in combination for treatment of BV in women of reproductive age (15 - 50 years old). There was no limit for the presence of a control group. Duplicates, non-English papers *in vitro* animal models, studies that reported co-infected by other pathogens like *Candida* spp. or *Trichomonas vaginalis* were excluded. The bibliography of the included trials was also thoroughly investigated.

Quality assessment

The Jadad scale [12] was applied for assessing the quality of the included trials. Two authors independently examined the quality of papers. If there were discrepancies between the authors, it would be resolved by consensus or consultation with a third party. We also considered "intention-to-treat" analysis and "baseline comparability".

Data extraction

The general characteristics and information, including the first author, location of the study, date of study, patients age, type of intervention, the treatment that control group received, number of participants in each group, duration of treatment, dropout rate (%), results and side effects, were extracted. Data extraction was independently done by two authors.

Results and discussion

The initial search yielded 171 articles, of which, 56 duplicated articles were deleted. Out of the 115 remaining papers, 97 were excluded following assessment of the title and abstract. Eighteen full-text articles were further reviewed. We excluded 5 studies because patients were co-infected by other pathogens like *Candida* spp. or *Trichomonas vaginalis*. After full-text review and verification, 13 papers were qualified for inclusion. Figure 1 demonstrates the search results and article selection process.

Quality assessment of the included studies is shown in Table I. All clinical trials were randomized and included a control group, but the randomization method was not mentioned in four papers. In one study, the randomization method was not correct. Blinding was not considered in 4 studies. All studies reported loss to follow-up. Only in one study, intention-to-treat analysis was done.

Detailed characteristics of the included studies are listed in Table II. All of the studies enrolled patients of reproductive age (i.e. 15 - 50 years old) and in all cases, the control group received different forms of metronidazole. Duration of intervention ranged from 5 to 7 days.

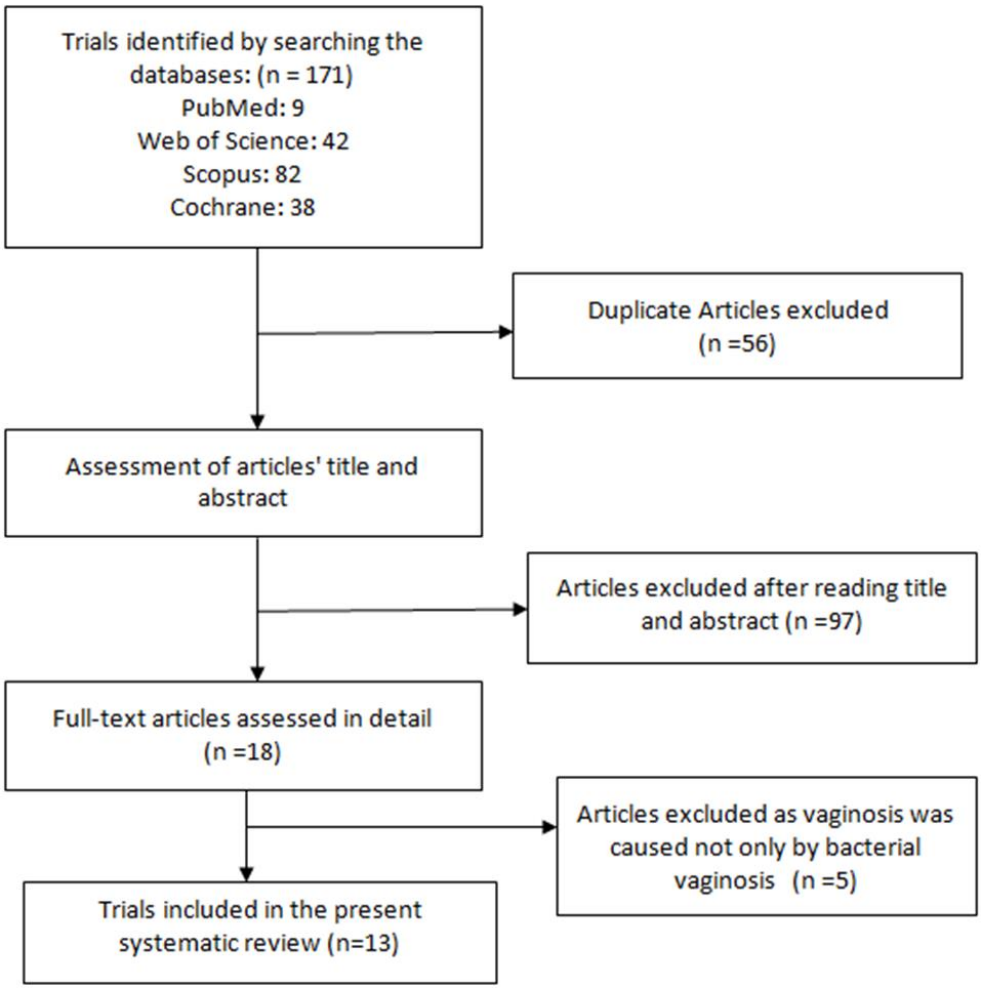

Figure 1.
The process of selection of the included trials

Table I
Quality assessment of the studies included in this systematic review

First author	Randomization			Blinding			Report of loss to follow up	Baseline comparability	Intention-to-treat analysis
	Mention randomization	Appropriate Method	Inappropriate Method	Mention blinding	Appropriate Method	Inappropriate Method			
Hafizi-Moori, M. [10]	+	?	-	-	-	-	+	+	?
Azadpour Motlagh, A. [11]	+	+	-	+	+	-	+	+	-
Leite, SRRF. [5]	+	+	-	+	+	-	+	+	+
Baery, N. [12]	+	?	-	+	+	-	+	+	?
Jafarnezhad, F. [13]	+	-	+	+	+	-	+	+	-
Mohammadzadeh, F. [14]	+	+	-	+	+	-	+	+	-
Masoudi, M. [15]	+	+	-	+	+	-	+	+	?
Simbar, M. [16]	+	?	-	-	-	-	+	+	?
Abdali, K. [17]	+	+	-	+	+	-	+	+	?
Asadi, M. [18]	+	?	-	-	-	-	+	+	?
Pazhohideh, Z. [19]	+	+	-	+	+	-	+	+	-
Sosto, F. [20]	+	+	-	-	-	-	+	+	-
Mohammad-Alizadeh-Charandabi, S. [8]	+	+	-	+	+	-	+	+	?

"+" shows that the specific criteria was noted in the study; "-" indicates the absence of the criteria; "**?**" denotes that it was not possible to evaluate the specific criterion.

Table II

Characteristic of the 13 trials included in this systematic review

First author, country, year	Patients age range (years old)	Diagnosis method	Type of intervention	Control group	Duration of treatment	Drop out % (Int., Con.)	Results	Adverse event in trial group (%)
Hafizi-Moori M, 2010, Iran [13]	18 - 44	Patients' complaints, Amsel clinical criteria	Micosin® vaginal cream (made of garlic) (n = 50)	Metronidazole vaginal gel (n = 50)	7 days	0%	The two groups after treatment had similar results in terms of improvement of patients' complaints and Amsel criteria score	Nausea (18%) Pruritus (28%) Drug-related odour (10%) Irritation (10%) Vomiting (6%) Lower abdominal pain (4%) Vertigo (2%)
Azadpour Motlagh A, 2018, Iran [14]	15 - 49	Amsel clinical criteria, Nugent microscopic criteria	oral metronidazole + *Prangos ferulacea* vaginal cream (n = 50)	Oral metronidazole + placebo vaginal cream (n = 50)	7 days	10%, 10%	The two groups after treatment had similar results in terms of patients' complaints, Amsel clinical criteria score and microscopic criteria Nugnt	Nausea, and metallic taste (Overall 16%)
Leite SRRF, 2011, Brazil [5]	18 - 40	Amsel clinical criteria, Nugent microscopic criteria	pepper tree extract gel (n = 137)	Metronidazole gel 0.75% (n = 140)	7 days	7%, 9%	Total cure rate was 12.4% in intervention group and 56.4% in control group ($p < 0.001$)	Heat (307%) Rash (0.7%) Itching (3.7%) Burning (3%) Abdominal pain (8.1%)
Baery N, 2018, Iran [15]	18 - 50	Amsel clinical criteria	vaginal suppository of Forzejeh® (*Tribulus terrestris* + *Myrtus commnuis* + *Foeniculum vulgare* + *Tamarindus indica*) (n = 64)	Vaginal suppository of metronidazole (n = 63)	7 days	10%, 9%	Fozejeh® was as effective as metronidazole with respect to the amount and odour of discharge, Amsel criteria score, pelvic pain and cervical inflammation	No serious side effect
Jafarnezhad F, 2017, Iran [16]	15 - 49	Amsel clinical criteria	Phytovagex® vaginal suppository (*Nigella sativa*) + placebo tablet (n = 31)	Metronidazole oral tablet + placebo vaginal suppository (n = 31)	7 days	0%, 16%	Treatment success rate was 74.2 % for Phytovagex and 69.2% for metronidazole group ($p = 0.68$)	Mild burning (12.9%)
Mohammadzadeh F, 2014, Iran [17]	18 - 44	Amsel clinical criteria, Nugent microscopic criteria	Garlic tablet (n = 60)	Metronidazole tablet (n = 60)	7 days	14%, 14%	Treatment success in garlic group (63.3%) was higher than metronidazole (48.3%), however, non-significant ($p = 0.141$)	More frequent side effects in metronidazole group than the intervention group
Masoudi M, 2016, Iran [18]	18 - 40	Amsel clinical criteria	Vaginal gel *Berberis vulgaris* 5% with metro-nidazole base (n = 40) and Vaginal gel *Myrtus communis* 2% with metronidazole (n = 40)	Metronidazole vaginal gel 0.75% on bacterial (n = 40)	5 days	0%	Cure rate in both intervention groups was higher than metronidazole alone ($p < 0.001$) there was no significant difference between to intervention groups ($p = 0.18$)	Not mentioned
Simbar M, 2008, Iran [19]	18 - 40	Amsel clinical criteria Nugent microscopic criteria	*Z. multiflora* vaginal cream (n = 45)	Metronidazole vaginal gel (n = 45)	5 days	4%, 2%	There was no significant difference between intervention and control groups ($p > 0.05$)	Vaginal burning (14%)

First author, country, year	Patients age range (years old)	Diagnosis method	Type of intervention	Control group	Duration of treatment	Drop out % (Int., Con.)	Results	Adverse event in trial group (%)
Abdali K, 2015, Iran [20]	Reproductive age	Nugent microscopic criteria	*Z. multiflora* cream + placebo tablet (n = 70)	Oral metronidazole tablet + placebo cream (n = 70)	7 days	0%	There was no significant difference between intervention and control groups ($p > 0.05$)	Irritation
Asadi M, 2016, Iran [21]	18 - 44	Amsel clinical criteria	Mycocin® vaginal cream (*garlic* + *thyme*) (n = 60)	Metronidazole vaginal gel (n = 60)	7 days	0%	There was no significant difference between intervention (86.66% improvement) and control groups (78.33% improvement) ($p > 0.05$)	Not mentioned
Pazhohideh Z, 2018, Iran [22]	18 - 45	Amsel clinical criteria	*Calendula officinalis* cream (n = 40)	Metronidazole vaginal cream (n = 40)	7 days	0%	There was no significant difference between intervention and control groups. All patients cured	none
Sosto F, 2011, Italy [23]	Reproductive age	Amsel clinical criteria	Thymol + eugenol vaginal douche	Metronidazole suppository	7 days	0.9% (overall)	There was no significant difference between intervention (86.66% improvement) and control groups (78.33% improvement) ($p > 0.05$)	none
Mohammad-Alizadeh-Charandabi S, 2014, Iran [11]	18 - 49	Amsel clinical criteria	*H. perforatum* + placebo (n = 82)	Metronidazole + placebo (n = 80)	5 days	0%	There was no significant difference between intervention (82% improvement) and control groups (85% improvement) ($p = 0.574$) except less itching in intervention group ($p = 0.018$)	Vaginal irritation at first day (13%), nausea, vomiting, dizziness and vaginal dryness

Int. = intervention; Con. = Control

Effects of vaginal suppository of *Foeniculum vulgare*, *Tribulus terrestris* and *Myrtus communis* *vs.* metronidazole vaginal suppository

Baery *et al*. conducted a trial examining the effect of a vaginal suppository containing a combination of *Foeniculum vulgare*, *Tribulus terrestris* and *Myrtus communis* recommended by the Persian herbal medicine, in comparison to metronidazole, and found no difference in the amount of discharge ($p = 0.33$) and odour discharge ($p = 0.18$), Amsel's criteria, pelvic pain ($p = 0.28$) and cervical inflammation ($p = 0.14$) between the two treatments. However, significant differences were observed between the two groups concerning the presence of clue cells ($p < 0.001$), Gram-positive bacteria ($p < 0.001$), pH ($p < 0.001$), Whiff test ($p < 0.001$) on the 14th day of the trial. Comparison of data obtained before and after the trial showed a significant improvement in both clinical symptoms and laboratory parameters in both groups. However, no statistically significant difference was seen between the two groups regarding the clinical symptoms or the laboratory assessments after the trial period [15].

Effects of pepper vaginal gel *vs.* metronidazole gel

Brazilian women with BV were divided into two groups to receive either 0.75% metronidazole gel (n = 140) or pepper extract gel (n = 137). The cure rate based on Amsel's criteria, was 21.2% in women treated with pepper tree extract and 62.1% in women treated with metronidazole ($p < 0.001$). The cure rate based on Nugent's score alone revealed that 13.9% were cured in the pepper tree extract group and 56.4% in the metronidazole group ($p < 0.001$). Total cure (calculated using the two criteria) was 12.4% in the extract and 56.4% in the metronidazole group ($p < 0.001$). Comparison of data obtained before and after the trial showed improvement for both clinical symptoms and laboratory parameters in both groups [5].

Effects of *Prangos ferulacea* vaginal cream plus oral metronidazole *vs.* oral metronidazole

One-hundred women with BV were randomized into two groups to receive oral metronidazole plus *Prangos ferulacea* vaginal cream (group A) or oral metronidazole plus a placebo (group B) vaginal cream for seven consecutive days. Comparison of data obtained before and after the treatment period, showed a significant

improvement in patients' complaints (abundant discharge ($p < 0.001$) and malodour ($p < 0.001$), Amsel clinical criteria (gray homogeneous discharge ($p < 0.001$), pH > 4.5 ($p < 0.001$), positive Whiff test ($p < 0.001$), clue cell 20 ($p < 0.001$)) and microscopic criteria Nugent ($p < 0.001$). However, comparison between the two groups showed no significant difference regarding the mentioned parameters. 78% of women in group A and 30% of women in group B totally recovered by the end of the fourth day. Inter-group comparison showed a significant difference with further improvement in metronidazole combined with *Prangos ferulacea* group (A) [14].

Effects of *Zataria multiflora* vaginal cream *vs.* metronidazole tablet/vaginal gel

Two trials assessed the effect of *Z. multiflora* on BV. In the study performed by Simbar *et al*., the patients were randomly assigned into two groups of *Z. multiflora* vaginal cream and metronidazole vaginal gel. Complications such as vaginal discharge, amine odour, dyspareunia, hypogastric pain, coitus, dysuria and malodour, were relieved significantly in both groups except for itching in *Z. multiflora* group. Comparison of the two groups showed no significant differences in Amsel's criteria. The relative risk (RR) was 1.53, suggesting that both treatments had a comparable effect based on Amsel's criteria in the treatment of BV. The side effect of vaginal burning was higher in *Z. multiflora* group compared to the metronidazole group ($p < 0.001$) [19].

In the study performed by Abdali *et al*., the efficacy of vaginal *Z. multiflora* was compared with oral metronidazole tablet. Statistical comparison of the data obtained before and after the treatment revealed that *Z. multiflora* had a significantly better effect in terms of clinical symptoms, including foul-smelling discharge, itching, vaginal discharge and intercourse pain. However, there was no statistically significant difference in all clinical symptoms between *Z. multiflora* and metronidazole after the intervention period. Also, no statistically significant difference in Gram staining between the two groups was found. Side effects like metallic taste, nausea and dizziness were more frequent in metronidazole group, while the irritation was more common in *Z. multiflora* group [20].

Effects of oral garlic *vs.* oral metronidazole

Mohammadzadeh *et al.* randomized 120 women with BV, into two groups: garlic tablet and oral metronidazole. The clinical improvement, as evaluated based on the Amsel's criteria, was significantly higher in the garlic-treated group (70%) compared to the metronidazole group (48.3%) ($p < 0.05$). Improvement in laboratory parameters, as assessed based on Nugent criteria, was reported in 68.3% of the patients treated with garlic compared to 55% of subjects in metronidazole group ($p > 0.05$). Success rate was considered if both clinical and laboratory parameters improved. The treatment success rate in the garlic group (63.3%) was higher than the metronidazole (48.3%) group, although the difference was not statistically significant. Patients in the metronidazole group (33%) reported side effect more frequently than the garlic group (15%) ($p = 0.032$) [17].

In the second study, Hafizi-Moori *et al*. included 100 women with BV randomized into two groups that received Micosin® vaginal cream (containing garlic) or metronidazole vaginal gel. Comparison of data obtained before and after the treatment period, showed a significant decrease in patients' complaints and Amsel's clinical criteria score (gray homogeneous discharge ($p < 0.001$), pH < 4.5 ($p < 0.001$), positive Whiff test ($p < 0.001$), clue cell 20 ($p < 0.001$)). However, comparison between the two groups showed no significant difference of the mentioned parameters. Response to treatment as assessed based on Amsel's clinical criteria, showed 80% improvement in Micosin and 70% improvement in metronidazole treated subjects ($p < 0.005$) [13].

In Asadi *et al*. study, 120 women were randomly designated into two groups of 60 to receive Micosin® vaginal cream or metronidazole vaginal gel for 7 days. The patients' complaints and clinical Amsel's criteria score were improved in both groups after treatment. Also, the two groups were compared with respect to clinical Amsel's criteria and the patients' complaints, 7 days after completion of the treatment period; the results showed a decrease in the patients' complaints and clinical Amsel's criteria score in both groups. However, no significant difference was observed between the two groups in clinical improvement based on Amsel's criteria score [21].

Effects of *Hypericum perforatum* L. *vs.* metronidazole

Mohammad-Alizadeh-Charandabi *et al*. compared the effect of vaginal *H. perforatum* with vaginal metronidazole against BV. Odds ratio for malodour was 1.5 (95% CI: 0.2 to 9; $p = 0.873$), for burning 2.9 (95% CI: 0.3 to 28.4; $p = 0.371$), and for lower abdominal pain 1.1 (95% CI: 0.4 to 3; $p = 0.873$), indicating that the mean score for all the mentioned parameters in *H. perforatum* group was similar to that of the metronidazole group. However, odds ratio for itching was 0.3 (95% CI: 0.1 to 0.8; $p = 0.026$) indicating that the mean frequency of itching was significantly lesser in the *H. perforatum* group than the metronidazole group. There was less frequent discharge in the *H. perforatum* group compared to the metronidazole group (4 *vs.* 15%, $p = 0.013$). Also, the frequency of pH > 4.5 was higher in the *H. perforatum* group compared to the metronidazole group (60 *vs.* 36%, respectively; $p = 0.003$). The BV recurrence was 9% in the *H. perforatum* group but

13% in the metronidazole group (p = 0.447). The RR for cure of BV (RR = 0.9; 95% CI: 0.6 to 1.3; p = 0.574), presence of the clue cells (RR = 1.3; 95% CI: 0.9 to 1.7; p = 0.153), and positive Whiff test (RR = 0.8; 95% CI: 0.4 to 1.3; p = 0.31) suggested no statistically significant difference between *H. perforatum* and metronidazole. Satisfaction scores after treatment in the *H. perforatum* group and the metronidazole group were as follows: 67 *vs*. 35% very satisfied, 19 *vs*. 33% satisfied, 11 *vs*. 13% unsure and 3 *vs*. 19% unsatisfied [11].

Effects of *Nigella sativa vs*. oral metronidazole

Only one trial assessed the effect of *N. sativa* on BV. Jafarnezhad *et al*. randomized 57 patients with BV into two groups that received either Phytovagex® vaginal suppository 1% (containing *N. sativa*) once a day or 250 mg oral metronidazole twice a day for a week. A statistically significant difference was seen between data obtained before and after treatment, in both groups in all Amsel's criteria scores (grey hemogenin discharge, clue cell in wet expansion, pH ≤ 4.5 and positive Whiff test), itching, burning, dyspareunia and inflammation. Intergroup comparison showed significant differences in all above-mentioned parameters. The treatment success was 74.2% for Phytovagex® and 69.2% for metronidazole (p > 0.05) [16].

Effects of *Berberis vulgaris* in metronidazole base, *Myrtus communis* L. in metronidazole base and metronidazole alone

Masoudi *et al***.** compared three groups treated with *B. vulgaris* in metronidazole base, *M. communis* in metronidazole base and metronidazole alone; the study was done on 120 women (18 - 40 years old) with BV. Comparison of the three groups showed a statistically significant difference in the cure rate among the three groups (p < 0.001). It was indicated that both *M. communis* in metronidazole base (p < 0.001) and *B. vulgaris* in metronidazole base (p < 0.001) were more efficacious than metronidazole alone. Comparison of the three groups showed no significant differences in terms of improvement of clinical symptoms of BV such as vaginal burning (p = 0.39), itching (p = 0.48), redness (p = 0.36), dyspareunia (p = 0.10), ague (p = 0.32), dysuria (p = 0.78) and dysmenorrhea (p = 0.90). No recurrence of infection occurred in *Berberis vulgaris* or *Myrtus communis* in metronidazole base groups while 12 patients (30%) in the metronidazole group had reported infection recurrence during a three-week follow-up [18].

Effects of *Saugella lavanda* Attiva *vs.* metronidazole suppository

In Sosto *et al*. study, group A received thymol + eugenol vaginal douche once a day for seven days and group B received one metronidazole vaginal suppository once at night for one week plus econazole once at night for three days. The two groups were not different with respect to all symptoms including burning, vulvovaginal erythema, oedema, vaginal dryness, dyspareunia and vaginal discharge; however, itching was better controlled in B group in comparison to A group [23].

Effects of *Calendula officinalis vs*. metronidazole vaginal cream

A series of studies depict the complex role of *Calendula officinalis* and its bioactivity [42]. In Pazhohideh *et al*. study, women with BV were divided into two groups that received either methanolic extract of *C. officinalis* vaginal cream or metronidazole vaginal cream for seven days. All subjects in both groups were without symptoms 1 week after treatment completion [22].

Bacterial vaginosis is considered the most common vaginal infection [24]. Metronidazole, the first-line antibiotic to treat BV, has shown a 70 - 80% success rate, but a 30% recurrence rate within three months, was reported [25]. Also, metronidazole is associated with several side effects including a metallic taste, nausea and transient neutropenia [15].

Clindamycin is the second choice in treatment of BV and has side effects such as abdominal cramps, colitis, nausea, vomiting, diarrhoea, and elevated liver enzymes [17]. Therefore, it is important to find novel agents for the treatment of BV. In this systematic review, we presented randomized controlled trials (RCTs) done to investigate the efficacy of application of herbal medicines in treatment of BV. Hence, we introduced 13 herbal medicines that were examined in this regard.

A suppository containing including *Foeniculum vulgare*, *Tribulus terrestris* and *Myrtus communis*, recommended by the Persian herbal medicine, was as effective as metronidazole suppository, regarding the amount of discharge. Pepper tree was more effective than placebo but less effective than metronidazole.

Z. multiflora was found to be as effective as oral or vaginal metronidazole against both clinical symptoms as well as laboratory parameters [20, 26]. The main components *of Z. multiflora* essential oil are thymol (22.3%), followed by linalool (6.2%), terpinene (6.4%), 1,8-cineol (5.3%), and carvacrol (3.1%) [27]. Anti-bacterial and antifungal activities of thymol and carvacrol were reported in several studies [20].

Z. multiflora has shown the maximum level of antibacterial activity with the MICs of 0.625 and

1.25 mg/mL for *Salmonella typhimurium* and *Listeria monocytogenes*, respectively [28]. Ziaee *et al*. reported that the antibacterial activity *Zataria multiflora* Boiss. essential oil against *Lactobacillus curvatus* is mediated *via* affecting the membrane permeability and cell integrity [29].

In another trial [20], *Z. multiflora* and metronidazole caused a significant decrease of the clinical symptoms. In contrast to Abdali *et al*. study, improvement in itching symptom did not reach significant level in a study performed by Simbar *et al*. [26].

H. perforatum L. vaginal gel 3% was shown to be as effective as metronidazole vaginal gel 0.75% in preventing BV recurrence, and in treating this infection [11]. *H. perforatum* showed antibacterial [30-33], and anti-inflammatory activities *in vitro* [25, 34]. *H. perforatum* alcoholic extracts (methanolic/ethanolic) were shown to be more effective than the aqueous extracts; also, *Hypericum perforatum* exhibits a lower antibacterial activity against Gram-negative bacteria than Gram-positive ones [35].

Nigella sativa effects against BV were comparable to those of metronidazole in alleviating both clinical symptoms and laboratory findings [16]. *Nigella sativa* is known for its antimicrobial activity [36], especially against anaerobic bacteria (*Clostridium difficile, Clostridium perfringens, Bacteroides fragilis* and *Bacteroides thetaiotaomicron*) [37] and Gram-positive cocci (*Staphylococcus aureus* ATCC 25923 and *Staphylococcus epidermidis* CIP 106510) [38].

Moreover, garlic was found to be as effective as oral or vaginal metronidazole in improving both clinical and laboratory findings. Garlic has antimicrobial activities against both Gram-positive and Gram-negative micro-organisms [39].

Crude extracts of garlic has antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) strains [40] and standard strains of *Escherichia coli* and *Staphylococcus aureus* [39].

In Houshmand *et al*. trial, the extract of *Myrtus communis* showed different effects at different concentrations against aerobic and anaerobic bacteria [41]. Masoudi *et al.* reported that the antibacterial activity of *M. communis* is mediated through increased oxygen free radicals and lipid peroxidation, which can disrupt the bacterial cell wall.

According to other results, oral metronidazole plus oral *Prangos ferulacea* resulted in a faster improvement compared to metronidazole plus placebo [43]. However, it is not possible to precisely attribute the healing effects to one of the drugs in combination. Future studies are needed to examine the probable synergistic effects between metronidazole and herbal medicines.

Limitations, strength and suggestions for future research

There were some limitations in conducting the present review. Only one trial appropriately reported information on the intention-to-treat analysis [5].

For some trials [13, 15, 19, 21], it was not possible to evaluate the specific criteria for randomization and in one study [16] randomization was conducted inappropriately. Also, some trials [13, 19, 23] used no blinding method and in some studies, patients were not followed up to detect recurrence of their disease [14].

Conclusions

Herbs such as *H. perforatum*, *Z. multiflora*, *B. vulgaris* and garlic, were found to be as effective as metronidazole with fewer side effects. These findings must be interpreted with caution in light of the limitations of the above-noted trials like the low methodological quality. Health providers might prescribe these herbs to patients, especially those with metronidazole-resistant infections, and those who are sensitive towards the side effects of metronidazole.

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