

# Evaluation of the Efficacy of Medicinal Plants in Treating Bacterial Vaginosis: A Comprehensive Systematic Review of Interventional Studies

## Abstract

**Background:** Bacterial Vaginosis (BV) is the most prevalent cause of vaginal infection among women. This study aimed to summarize the evidence related to the effectiveness of medicinal plants as an alternative therapy for the management of BV. **Materials and Methods:** PubMed, Scopus, Cochrane Library, Web of Science, and Medline PubMed were systematically searched. Moreover, we searched Google Scholar to explore the possible effects of herbal treatments on BV in women of childbearing age up to 2022. All randomized clinical trials investigating the effects of medicinal plants as oral or vaginal monotherapy or in combination for BV treatment in women of childbearing age were included in this systematic review. **Results:** In total, 20 studies comprising 2685 participants were included in our review. The results show that combinations of herbal medicines such as *Prangos ferulacea*, *Berberis vulgaris*, *Myrtus communis*, and *Quercus Brantii* with metronidazole can have better results in the treatment of BV. Moreover, the main results show that some medicinal plant products alone such as Forzejehe (*Tribulus terrestris* + *Myrtus communis* + *Foeniculum vulgare* + *Tamarindus indica*), *Zataria multiflora*, and *Calendula officinalis* had therapeutic effects similar to metronidazole. Propolis and Brazilian pepper tree (*Schinus*) were effective in the treatment of BV, but they have less therapeutic effect than metronidazole. **Conclusions:** To reduce the complications caused by chemical treatments and also the resistance of patients to these treatments, it seems necessary to use supportive treatments along with chemical drugs after the necessary approvals have been obtained.

**Keywords:** Bacterial, complementary therapies, medicinal, medicine, Persian, plants, systematic review, vaginosis

## Introduction

Reproductive tract health is an important part of women's health, especially women of childbearing age.<sup>[1]</sup> Bacterial Vaginosis (BV) can endanger the health of this organ. BV is the most common cause of vaginal infections in women of childbearing age.<sup>[2]</sup> BV is caused by the growth of anaerobic microorganisms such as *Gardnerella spp.*, *Atopobium vaginae*, and *Prevotella spp.*, as well as a decrease in the level of normal vaginal flora like *Lactobacillus*. Anaerobic bacteria are not normally found in the vagina of healthy women, while their amount increases to 100% in patients.<sup>[3]</sup> The risk factors of BV are frequent vaginal douching and frequent sexual activity that cause alkalizing of the vagina.<sup>[4]</sup> The prevalence of BV is high and its prevalence is 4% in asymptomatic women and 61% in women who are referred to the clinic due to Sexually Transmitted Diseases (STDs).<sup>[5]</sup> Symptoms

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of BV are irritation and itching of the vulva and white and grayish vaginal discharge with an unpleasant odor.<sup>[6]</sup> Definitive and standard diagnosis of BV is to have the three clinical criteria of Amsel including: pH > 4.5, positive Whiff test, white-gray vaginal discharge, and the presence of clue cells in smear and gram staining.<sup>[7]</sup> This plant had a better effect than metronidazole vaginal gel in the treatment of patients.<sup>[5]</sup> Common antibiotics such as clindamycin and metronidazole are widely used to treat vaginosis and metronidazole is the first line of treatment of BV.<sup>[3]</sup> However, it has side effects including a metallic taste in the

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mouth, digestive disorders, abdominal pain and cramps, nausea and vomiting, drowsiness, dizziness, hallucinations and delusions, exacerbation of schizophrenia symptoms, mania attack, and decreased gonadotropin, testosterone, and spermatogenesis hormones.<sup>[8]</sup> There have been reports of metronidazole being carcinogenic, drug resistance to it, and repeated relapses due to the formation of *Gardnerella vaginalis* biofilm in the vagina.<sup>[9]</sup>

Because of the side effects of chemical drugs and patient resistance to treatment,<sup>[10]</sup> it is important to find new treatments that have fewer side effects. Moreover, patients' willingness to use medicinal plants has led researchers to investigate the effectiveness of these drugs on various diseases, including BV.<sup>[11]</sup> In addition, a large number of women use natural herbal treatments such as garlic and tea tree oil intravaginally.<sup>[12]</sup> Therefore, we decided to evaluate the herbal treatments for BV. There are various studies with different plants in this field, such as the examination by Shabani et al.<sup>[13]</sup> which scrutinized the impact of *Berberis vulgaris* emollient on 80 women with BV. This plant had a better effect than metronidazole vaginal gel in the treatment of patients,<sup>[13]</sup> but in the study by Leite et al.,<sup>[14]</sup> the effect of *Brazilian pepper* tree (*Schinus*) extract on 177 women suffering from BV were examined. The extract of this plant was less effective than metronidazole vaginal gel. In another study conducted by Simbar et al.,<sup>[15]</sup> the effect of *Zataria multiflora* vaginal cream on 90 married women with BV was investigated. This plant was as effective as metronidazole in treating patients. Different studies with different interventions based on medicinal plants have presented different results in the treatment of BV.<sup>[16,17]</sup> Therefore, this study aimed to summarize the evidence related to the effectiveness of medicinal plants as an alternative therapy for the management of BV.

## Materials and Methods

What are the effects of complementary/alternative medicine in patients with BV? This systematic review study was based on PRISMA and its protocol was registered with the code CRD42022344146 on the PROSPERO website. The objective of this investigation was to methodically scrutinize the substantiation of the efficacy of therapeutic flora in alleviating BV. A Participants, Intervention, Comparators, and Outcomes (PICO) approach was used to rate the studies for eligibility. We adopted the following criteria for including the articles in our study: P: women within the reproductive age range, I: botanical remedies used orally or vaginally, C: other common treatments, O: vaginal PH, whiff test positive, vaginal discharge, mal odor.

Consequently, we conducted a comprehensive exploration in the databases of PubMed, Scopus, Cochrane Library, and Web of Science systematically for studies investigating the possible effects of medicinal plants on BV in women of reproductive age and published up to 2022. The keywords for the search were ("BV" OR "bacterial vaginitis"

OR "bacterial vaginosis") AND ("herbal medicine" OR "plant extract" OR "medicinal plant" OR herb OR "plant medicinal" OR "herbal drug" OR "herbal product" OR "Persian medicine" OR "traditional medicine" OR "complementary medicine" OR "alternative medicine" OR "Integrative Medicine"). In addition, the search was done in the Google Scholar database. Therefore, our search period was from January 2000 to December 2022. Clinical trial registries, thesis, and pre-print services were searched to access gray literature. The search was conducted on English-language articles or articles with English abstracts. Two authors (M E and Z S) performed the search and data extraction independently, and discrepancies between authors were resolved through consensus with a third author (M K).

The inclusion criteria were all randomized trials that investigated the effect of botanical remedies orally or vaginally administered as a sole therapy or in conjunction with the management of BV in women within the reproductive phase (18–50 years of age).

In addition, the exclusion criteria were replicates, animal studies, laboratory studies, and studies with the cause of disease of other pathogens such as *Candida* species or *Trichomonas vaginalis*. All the titles and abstracts of the studies were screened and irrelevant studies were removed, all the retrieved studies were read in full after the screening, and the full text of all remaining studies was read in detail, eligibility was evaluated by the researchers, and differences were resolved through discussion. The characteristics and general information extracted by the authors included first author, place of study, year of publication, type of study, type of intervention, type of comparison, method of drug administration, follow-up period of patients, characteristics of participants, and output data and final result.

The Jadad scale<sup>[18]</sup> was employed to assess the caliber of the encompassed experiments. Quality assessment was done by the first author and checked again by the corresponding author to ensure that no errors occurred. If no agreement was reached, it was resolved through discussion.

## Ethical considerations

This study was approved by the Research Ethics Committee of Kerman University of Medical Sciences. This manuscript has no plagiarism. The results of the analysis were completely honest. Any data fabrication has been avoided. This article does not contain any studies with human participants performed by any authors. This study was approved by the Ethics Committee of Kerman University of Medical Sciences with of ethics code (IR.KMU.REC.1400.547).

## Results

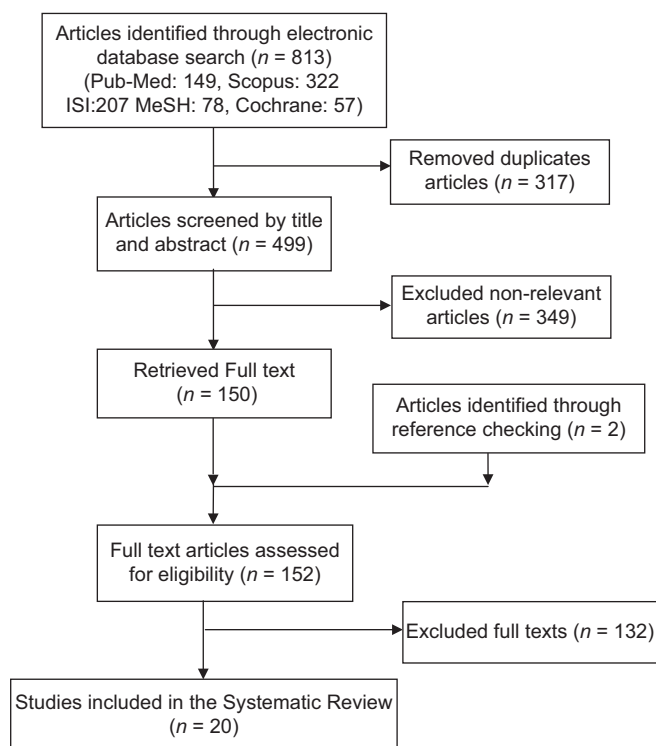
### Study identification

During the preliminary investigation, a total of 813 scholarly publications were acquired, out of which 314 redundant publications were eliminated. Subsequently, from the remaining pool of 499 publications, 349 publications were excluded following an assessment of their respective titles and abstracts. In total, 150 full-text articles were reviewed. We disregarded 132 investigations due to the presence of patients who had been afflicted with alternative microorganisms, such as *Candida* species or *Trichomonas vaginalis*, or because the study had been conducted in a controlled laboratory environment. After reviewing and confirming the full text, 20 eligible articles were included in this study. Figure 1 presents the findings of the investigation and the procedure for choosing scholarly publications.

### Study characteristics

The primary demographic and clinical attributes of the individuals as well as the methodologies of experiments encompassed in the comprehensive appraisal are outlined in Table 1.

Seven studies of clinical symptoms and Amsel's criteria, seven studies of clinical symptoms and Amsel and Nugent grading system, three studies of clinical symptoms alone, two studies of clinical symptoms and recovery rate, and one study of Amsel's and Nugent's criteria have been considered as outcomes.



**Figure 1: Papers search and review flowchart for selection of primary studies**

### Quality of studies

The quality assessment of the included studies is presented in Table 2. Every single clinical trial was subjected to randomization and encompassed a control group; however, the approach of randomization was not specified in ten papers. The aspect of blinding was not taken into account in three investigations. All studies documented individuals who were not available for follow-up. An intention-to-treat analysis was conducted in only one investigation.

According to Table 1, the main results show gel derived from *Berberis vulgaris* exhibited superior efficacy in the treatment of BV compared to the gel containing metronidazole. Moreover, a combination of herbal medicines such as *Prangos ferulacea*, *Berberis vulgaris*, *Myrtus communis*, and *Quercus Brantii* with metronidazole can have better results in the treatment of BV. In addition, the main results show that some medicinal plant products alone such as Forzejehe (*Tribulus terrestris* + *Myrtus communis* + *Foeniculum vulgare* + *Tamarindus indica*), *Zataria multiflora*, and *Calendula officinalis* had therapeutic effects similar to metronidazole. As can be seen in Table 2, Propolis and Brazilian pepper tree (*Schinus*) are effective in the treatment of BV, but they have less therapeutic effect than metronidazole.

### Discussion

This study evaluated the efficacy of medicinal plants in the treatment of BV and found that most of the studied medicinal plants have been effective in curing BV. Most of the studies were on *Berberis vulgaris* alone or in combination with other plants. It is believed to be more effective than metronidazole gel in treating BV. In two studies, *B. vulgaris* extract was used to treat BV. In the study by *Shabanian et al.*,<sup>[13]</sup> *B. vulgaris* extract was used compared to metronidazole gel. This intervention showed significantly higher symptom improvement in the *B. vulgaris* group than in the metronidazole group ( $p = 0.001$ ).<sup>[13]</sup> *Masoudi et al.*<sup>[19]</sup> used *B. vulgaris* extract in combination with metronidazole vaginal gel. The results of this investigation demonstrated a statistically significant disparity in the response to therapy among the analyzed groups ( $p > 0.001$ ), and the *B. vulgaris* drug in the metronidazole gel base group had a better response than the metronidazole gel alone when treated for BV. Patients who were given *B. vulgaris* in metronidazole gel base did not experience any relapse, whereas 30% of patients in the metronidazole group experienced relapse within three weeks of discontinuing the medication.<sup>[19]</sup> The fruit of *B. vulgaris* has antihistamine properties and contains vitamin C and acidic compounds. Thus, it can eliminate some vaginitis symptoms.<sup>[28]</sup> One of the most important active ingredients in *B. vulgaris* is berberine.<sup>[29]</sup> Berberine is a DNA ligand and has the ability to bind to DNA and affect the structure of bacterial DNA molecules.<sup>[30]</sup> It also inhibits cell division by using the FtsZ protein.<sup>[31]</sup>

Table 1: Characteristic of the 20 trials included in this systematic review

First Author's name	Country	Publication year	Type of Study	Type of product (s)	Type of comparison (Oral, Local)	Type of use (Oral, Local)	Follow-up time	Outcome measure	Participant characteristics	Main result
Nasrin Baery <sup>[2]</sup>	Iran	2018	Clinical trial	Forzeje (Tribulus terrestris + Myrtus communis + Foeniculum vulgare + Tamarindus indica)	Metronidazole sup.	Vaginal	14 Days	Symptoms/ Amsel Criteria	127 married Women (18–50 years)	Forzeje has a therapeutic effect the same as metronidazole.
Somayyeh Khasaaci <sup>[4]</sup>	Iran	2018	Clinical trial	Sucrose gel	Metronidazole	Vaginal	14 Days	Symptoms/ Amsel Criteria	70 married Women (15–45 years)	The therapeutic response difference was not significant between metronidazole and sucrose gel.
Farzan Jafarnezhad <sup>[9]</sup>	Iran	2017	Clinical trial	Phytovagx vaginal sup. (nigella sativa) + Placebo tablet	Metronidazole oral tablet + Placebo vaginal sup.	Vaginal/oral	17 Days	Symptoms/ Amsel Criteria	57 married Women (15–49 years)	Phytovagx and metronidazole had the same effect.
Mansour Masoudi <sup>[19]</sup>	Iran	2016	Clinical trial	Myrtus Communis vaginal gel, Berberis Vulgaris vaginal gel in metronidazole base	Metronidazole vaginal gel	Vaginal	3 weeks	Symptoms/ recovery rate	120 married Women (19–40 years)	Vaginal gel consisting of extracts of Myrtus communis or Berberis vulgaris in metronidazole base were more effective than metronidazole gel alone on BV.
Mahsa Sadat Mousavi <sup>[12]</sup>	Iran	2015	Clinical trial	Propolis vaginal cream	Metronidazole	Vaginal	7 Days	Amsel Criteria/ Cured rate/ Nugent Criteria	100 married Women	The therapeutic effect of propolis on BV is less than metronidazole.
Hojjat Eghbal <sup>[20]</sup>	Iran	2018	Clinical trial	Oregano, mint, summer savory	Metronidazole	Vaginal		Symptoms/ Amsel Criteria	80 married Women (18–44 years)	The herbal vaginal cream and metronidazole vaginal gel had similar therapeutic effects on BV.
Maryam Asadi <sup>[17]</sup>	Iran	2016	Clinical trial	Mycocin vaginal cream (made of garlic and thyme)	Metronidazole	Vaginal	14 Days	Symptoms/ Amsel Criteria/ Gram stain	120 married Women (18–44 years)	The garlic and thyme vaginal cream and metronidazole had similar effects on BV.
M. Simbar <sup>[15]</sup>	Iran	2008	Clinical trial	Zataria multiflora vaginal cream	Metronidazole gel	Vaginal	12 Days	Symptoms/ Amsel Criteria/ Gram stain	90 married Women (18–40 years)	Z. Multiflora vaginal cream is as effective as metronidazole in the treatment of BV.
Elham Afzali <sup>[21]</sup>	Iran	2020	Clinical trial	Quercus (Oak Gal) vaginal cream	Metronidazole gel	Vaginal	12 Days	Symptoms/ Amsel Criteria	84 married women (15–45 years)	Oak Gall vaginal cream was as effective and safe as metronidazole in the treatment of BV.

Contd...

Table 1: Contd...

First Author's name	Country	Publication year	Type of Study	Type of product (s)	Type of comparison	Type of use (Oral, Local)	Follow-up time	Outcome measure	Participant characteristics	Main result
Asieh Azadpour	Iran	2017	Clinical trial	Oral metronidazole + <i>Prangos ferulacea</i> vaginal cream	Oral metronidazole + placebo vaginal cream	Vaginal	14 Days	Symptoms/ Amsel Criteria/ Nugent Criteria	100 married women (15 to 49 years)	<i>Prangos ferulacea</i> vaginal cream accelerated the recovery of BV treatment.
Sakineh Mohammad-Alizadeh-Charandabi <sup>[11]</sup>	Iran	2014	Clinical trial	<i>Hypericum perforatum</i> + placebo of Metronidazole	Metronidazole + placebo of <i>Hypericum perforatum</i>	Vaginal	35 Days	Symptoms/ Amsel Criteria	162 married Women (18–49 years)	There was no statistically significant difference between <i>h. perforatum</i> and metronidazole in BV treatment.
Sheida Shabani <sup>[3]</sup>	Iran	2019	Clinical trial	<i>Berberis vulgaris</i> gel	Metronidazole gel	Vaginal	21 Days	Symptoms	80 married women (mean age of 34 years)	<i>Berberis vulgaris</i> gel was more effective than metronidazole gel in treating BV.
Mansour Masoudi <sup>[22]</sup>	Iran	2016	Clinical trial	<i>Berberis vulgaris</i> + metronidazole gel	Metronidazole gel	Vaginal	14 Days	Symptoms	100 married Women (18–40 years)	Adding <i>Berberis vulgaris</i> fruit extract to metronidazole improved the efficacy of BV treatment.
Hafzi Moori <sup>[16]</sup>	Iran	2010	Clinical trial	Micosin vaginal cream (made of garlic)	Metronidazole gel	Vaginal	14 Days	Symptoms/ Amsel Criteria	100 married Women (18–44 years)	There was no statistically significant difference between Mycocin vaginal cream and metronidazole in terms of BV treatment.
Farnaz Mohammadzadeh <sup>[23]</sup>	Iran	2014	Clinical trial	Garlic Tablet (Garsin)	Metronidazole oral	oral	10 Days	Symptoms/ Amsel Criteria/ Nugent criteria	120 married Women (18–44 years)	The therapeutic effects of garlic on BV were similar to that of metronidazole and metronidazole has more complications.
Zahra Pazhohideh <sup>[24]</sup>	Iran	2018	controlled trial	<i>Calendula officinalis</i> Vaginal Cream	Metronidazole Vaginal Cream	Vaginal	14 Days	Symptoms	80 married women (18–45 years)	The therapeutic effect of <i>C. officinalis</i> was the same as metronidazole.
Mansoureh Masoudi <sup>[25]</sup>	Iran	2017	clinical trial	<i>Myrtus communis</i> + Metronidazole gel	Metronidazole gel	Vaginal	12 Days	Symptoms/ recovery rate	80 married Women (18–40 years)	The combination of metronidazole and <i>M. communis</i> had a higher efficiency in BV treatment.
S.R.R.F. Leite <sup>[4]</sup>	Brazil	2011	clinical trial	Brazilian pepper tree ( <i>Schinus</i> )	Metronidazole	Vaginal	7 Days	Amsel Criteria/ Nugent criteria	277 Women (18–40 years)	The cure rate for BV using a vaginal gel from pepper tree extract was lower than the rate obtained with metronidazole gel.

Contd...

Table 1: Contd...

First Author's name	Country	Publication year	Type of Study	Type of product (s)	Type of comparison	Type of use (Oral, Local)	Follow-up time	Outcome measure	Participant characteristics	Main result
Atefeh Zare <sup>[26]</sup>	Iran	2018	clinical trial	Metronidazole tablet + <i>Quercus Brantii</i> vaginal cream	metronidazole tablet + placebo vaginal cream	Vaginal	14 Days	Symptoms/ Amsel Criteria/ Nugent criteria	176 married women (18–49 years)	The findings suggested better results for metronidazole + <i>Quercus brantii</i> vaginal cream compared to those of metronidazole + placebo.
Kakhkashan Baig <sup>[27]</sup>	India	2022	clinical trial	Oral <i>P. integerrima</i> capsule	oral metronidazole tablets	oral	30-34 Days	Symptoms/ Amsel Criteria/ Nugent criteria	62 women	<i>P. integerrima</i> showed an effect similar to metronidazole in treating BV with no adverse effects

This function of the plant can also be the reason for its good effect on BV. In the study by Masoudi *et al.*,<sup>[22]</sup> *B. vulgaris* and *Myrtus communis L.* in metronidazole base were used for BV treatment. The treatment response between the study groups showed a statistically significant difference ( $p < 0.001$ ). The groups that received *M. communis L.* and *B. vulgaris* in metronidazole base had a better response to BV treatment than the group that received metronidazole gel alone. Additionally, there was no significant difference between the *M. communis L.* and *B. vulgaris* groups ( $p = 0.18$ ).<sup>[22]</sup> In another study by Masoudi *et al.*,<sup>[25]</sup> *M. communis L.* was used for treatment. A group of patients was treated with a combination of *M. communis* and metronidazole gel, and the other group with metronidazole gel, the treatment response showed a significant difference between the two groups. The combination of metronidazole and *M. communis L.* had a better effect than metronidazole gel alone ( $p < 0.05$ ).<sup>[25]</sup> *B. vulgaris* contains active ingredients such as berberine, berberine, and palmitin, which have anti-inflammatory, antihistamine, and antimicrobial effects on BV. *M. communis L.* contains polyphenols, myrtucommulone (MC), semi-myrtucommulone (S-MC), 1, 8-cineole,  $\alpha$ -pinene, myrtenyl acetate, limonene, linalool, and  $\alpha$ -terpinolene, which are the most important compounds with biological activity. Clinical and experimental studies show that *M. communis L.* has a wider range of medicinal and therapeutic effects such as antioxidant, anticancer, antidiabetic, antiviral, antibacterial, antifungal, liver protection, and neuroprotective effects.<sup>[32]</sup> The antibacterial activity of *M. communis L.* is due to the increase of oxygen free radicals and lipid peroxidation, which can break down the cell walls of microorganisms.<sup>[33]</sup> The therapeutic effects of *M. communis L.* on BV can be attributed to its properties. In a study by Baery *et al.*,<sup>[2]</sup> vaginal suppositories based on Persian medicine consisting of the plants *Tribulus terrestris*, *Myrtus communis*, *Foeniculum vulgare*, and *Tamarindus indica* were used for treatment. The group that received vaginal suppositories based on Persian medicine and metronidazole experienced significant reductions in the amount and odor of discharge, Amsel criteria, pelvic pain, and cervical inflammation ( $p = 0.001$ ). There were no statistically significant differences between the metronidazole and Persian-based vaginal suppositories groups in terms of clinical symptoms or laboratory assessments.<sup>[2]</sup> Regarding the therapeutic effect of medicinal plants in this suppository, the following can be mentioned: therapeutic compounds made from *T. terrestris* are useful for the treatment of bacteria, fungi, and viral infections, especially in female infections<sup>[34]</sup> as well as the antibacterial effects of the plant,<sup>[33]</sup> both of which are consistent with the results of this study. In the study by Mohammadzadeh *et al.*,<sup>[23]</sup> oral garlic (*Allium sativum*) tablets were used, and the Amsel criteria were significantly reduced after treatment with garlic or metronidazole ( $p < 0.001$ ). The therapeutic effects

**Table 2: Jadad scale for reporting randomized controlled trials**

First author	Year	Randomization	Blinding	An account of all patients	Total
Nasrin Baery <sup>[2]</sup>	2018	1	2	1	4
Somayyeh Khazaeian <sup>[4]</sup>	2018	2	2	1	5
Farzan Jafarnezhad <sup>[9]</sup>	2017	1	2	1	4
Mansoureh Masoudi <sup>[19]</sup>	2016	2	2	1	5
Mahsa Sadat Mousavi <sup>[12]</sup>	2015	2	0	0	2
Hojjat Eghbal <sup>[20]</sup>	2018	1	1	1	3
Maryam Asadi <sup>[17]</sup>	2016	1	1	1	3
M. Simbar <sup>[15]</sup>	2008	1	1	1	3
Elham Afzali <sup>[21]</sup>	2020	2	2	1	5
Asieh Azadpour	2017	2	2	1	5
Sakineh Mohammad-Alizadeh-Charandabi <sup>[11]</sup>	2014	2	2	1	5
Sheida Shabani <sup>[13]</sup>	2019	2	0	1	3
Mansour Masoudi <sup>[22]</sup>	2016	1	2	1	4
Hafizi Moori <sup>[16]</sup>	2010	1	0	1	2
Farnaz Mohammadzadeh <sup>[23]</sup>	2014	1	1	1	3
Zahra Pazhohideh <sup>[24]</sup>	2018	2	1	1	z4
Mansoureh Masoudi <sup>[25]</sup>	2017	1	2	1	4
S.R.R.F. Leite <sup>[14]</sup>	2011	1	2	1	4
Atefeh Zare <sup>[26]</sup>	2018	2	2	1	5
Kahkashan Baig <sup>[27]</sup>	2022	2	1	1	4

of garlic on BV were the same as metronidazole ( $p = 0.141$ ). There was a significant difference between the two groups in terms of side effects. Metronidazole had more complications ( $p = 0.032$ ).<sup>[23]</sup> In the study by Moori and Majd, Micosin vaginal cream (made of garlic) was used for treatment.<sup>[16]</sup> The results of the study showed that after using Micosin and metronidazole vaginal gel, patients reported fewer complaints, and a significant decrease was observed in the clinical Amsel criteria ( $p > 0.05$ ). The clinical recovery rate for the Micosin group was 80%, while it was 70% for the metronidazole group. The study found no statistically significant difference between Mycocin vaginal cream and metronidazole in treating BV.<sup>[16]</sup> In the study by Asadi *et al.*,<sup>[17]</sup> Mycocin vaginal cream made of garlic and thyme (*Thymus vulgaris L.*) was used for treatment. According to this study, patients who used herbal vaginal cream and metronidazole vaginal gel reported fewer clinical complaints and showed a decrease in Amsel criteria. However, there was no significant difference between the two groups in terms of clinical improvement based on Amsel criteria ( $p < 0.05$ ).<sup>[17]</sup> The precise mechanism or mechanisms behind the antimicrobial activity of allicin and garlic extract have not been determined yet, although several mechanisms have been proposed to explain the antimicrobial activity of allicin. One of these mechanisms is the interference in the function of sulfhydryl or Thiol group proteins and enzymes. Allicin irreversibly inhibits SH proteases and NADP-dependent alcohol dehydrogenase. However, mammalian cells seem to be resistant to the effects of allicin. This resistance is due to the presence of glutathione inside mammalian cells, which can cancel the activity of allicin that enters the cell.

In other words, this is one of the reasons for the wide spectrum of antimicrobial activity of allicin without having adverse effects on the host. Interference in the function of SH group proteins is one of the most important biological activities of allicin. Of course, other mechanisms have been suggested, such as preventing the transcription of mRNA and affecting the synthesis of proteins and DNA.<sup>[35]</sup> According to a study by Simbar *et al.*,<sup>[15]</sup> patients who used Zataria multiflora vaginal gel reported fewer complications, and a decrease was observed in Amsel criteria after treatment with both *Z. multiflora* and metronidazole ( $p < 0.05$ ). The therapeutic effects of *Z. multiflora* vaginal cream and metronidazole vaginal gel in BV were similar. Moreover, some side effects of *Z. multiflora*, including nausea and vaginal dryness, were similar to metronidazole. *Z. multiflora* is one of the plants selected by the World Health Organization (WHO) for its antibacterial and antifungal effects,<sup>[36]</sup> which confirms the effect of this plant in the treatment of BV. According to a study, the antibacterial effect of *Z. multiflora* is related to its phenolic compounds, which include thymol and carvacrol. Thymol and carvacrol can affect the fatty acid composition of the membrane of microbial cells and cause a change in the permeability of the cell membrane.<sup>[37]</sup> Khazaeian *et al.*<sup>[4]</sup> investigated the effect of sucrose gel on BV and reported that vaginal sucrose gel and metronidazole vaginal gel did not have a significant difference in reducing the clinical complaints of patients. They reported an enhancement proportion of 85.7% for sucrose gel and 88.5% for metronidazole gel; the dissimilarity in the curative reaction was not considerable and statistically there existed no variation in malady

enhancement ( $p = 0.389$ ).<sup>[4]</sup> Sucrose gel has no antibiotic properties. Hence, it is not possible to resist it. Nevertheless, it is a type of nutrition for *Lactobacillus*. It was also shown in an animal model that it helps to shift vaginal flora from BV to *Lactobacillus*.<sup>[38]</sup> The existence of *Lactobacillus* is an important factor in the prevention of infection and they exhibit greater efficacy than antibiotics like metronidazole. Metronidazole hampers the proliferation of pathogenic bacteria, and concurrently, the proliferation of *Lactobacillus*. This may be one of the contributing factors to an inadequate response to therapy and subsequent recurrence.<sup>[39]</sup> Jafarnejhad *et al.*<sup>[9]</sup> investigated the effect of Phytovagex suppositories containing *Nigella sativa* on BV. The percentage of BV treatment success in women in the phytovagex vaginal suppository group was 74.2% and, in the metronidazole, the oral tablet group was 69.2%, which was not statistically significant ( $p < 0.05$ ).<sup>[9]</sup> *N. sativa*, due to its compounds such as thymol and carvacrol, has antibacterial properties against BV. Thymol and carvacrol exert their effect through changes in cell membrane permeability.<sup>[40]</sup> In addition, thymoquinone and dihydro-thymoquinone are other substances found in *N. sativa* that exert their effect by increasing the immunogen properties of T cells. Furthermore, thymoquinone prevents the formation of the biofilm of bacteria,<sup>[41]</sup> and Alves *et al.*<sup>[42]</sup> showed BV bacteria tendency to form biofilm and that most cases were observed in *Gardnerella vaginalis*. The investigation conducted by Zare *et al.*<sup>[26]</sup> regarding the impact of *Quercus brantii* on BV categorized the patients into two groups: Group A received a dosage of 500 mg of metronidazole tablet, while Group B was administered the identical tablet combined with a *Quercus brantii* cream applied vaginally. Following the interventions, notable disparities were observed between the two groups in relation to the emission of unpleasant odors and the Nugent score. Considering the overall recovery, it was determined that 50.0% of the patients in cohort A and 73.8% of those in Group B exhibited signs of being successfully treated. The findings implied that the utilization of metronidazole and *Quercus brantii* vaginal cream yielded superior outcomes in comparison to the usage of metronidazole and a placebo.<sup>[26]</sup> The investigation conducted by Afzali *et al.*<sup>[21]</sup> delved into the impact of *Quercus* on BV. After a span of 1-week postintervention, all female participants belonging to both experimental and control groups exhibited no signs of symptoms (vaginal itching and burning, unpleasant odor, dysuria, and dyspareunia) ( $p < 0.001$ ). The percentage of treatment in the oak group was 82.1 ( $n = 33$ ) and in the metronidazole group, it was 87.5 ( $n = 34$ ) ( $p = 0.56$ ). Oak Gall vaginal cream was as effective and safe as metronidazole in the treatment of BV.<sup>[21]</sup> In alternative investigations, the antimicrobial characteristic of the *Quercus* fruit on pathogenic microorganisms has been substantiated.<sup>[43]</sup> The mechanisms of antibacterial actions of *Q. brantii* remain elusive; however, certain investigations have unveiled that

the anti-bacterial activity encompasses intricate processes such as metabolic suppression as well as the restraints of the cellular enclosure, plasma envelope, genetic material, and protein fabrications.<sup>[26]</sup> Azadpour Motlagh *et al.*<sup>[44]</sup> explored the impact of *Prangos ferulacea* vaginal cream on expediting BV treatment. An assessment of patients' grievances, Amsel clinical measures, and Nugent microscopic measures revealed a notable disparity between pre-treatment and post-treatment stages in both cohorts. The result of the treatment involving oral metronidazole in conjunction with *P. ferulacea* vaginal cream was determined to be 94% on the basis of the Amsel clinical measures and 88% according to the Nugent microscopic measures, while the outcome of the treatment involving oral metronidazole alongside placebo vaginal cream was determined to be 94% on the basis of the Amsel measures and 86% in accordance with the Nugent measures. No complications were observed in any of the two studied groups,<sup>[44]</sup> which could be due to the antioxidant and antimicrobial<sup>[45]</sup> properties of this plant, which have been confirmed in other studies. The antioxidant property of *P. ferulacea* is due to the presence of phenolic compounds such as monoterpenes, sesquiterpenes, coumarines, flavonoids, alkaloids, tannins, saponins<sup>[45]</sup> and the plant's antibacterial quality is likely due to its ability to prevent oxidized compounds from forming or reacting with sulfhydryl groups.<sup>[46]</sup> Mohammad-Alizadeh-Charandabi *et al.*<sup>[11]</sup> conducted a study to investigate the effect of *Hypericum perforatum L.* on BV and compared it with metronidazole. The study lasted for 10–12 days, and the recovery rate was 82% in the *H. perforatum* group and 85% in the metronidazole group.<sup>[11]</sup> The antibacterial and anti-inflammatory<sup>[47,48]</sup> properties of geranium have also been shown in other studies. In the study by Pazhohideh *et al.*,<sup>[32]</sup> which compared *Calendula officinalis* with metronidazole in the treatment of BV, the result was that 1 week after the treatment in both groups, none of the symptoms such as burning, itching, or dyspareunia were present. *C. officinalis* was effective in treating patients with BV and no complications were observed in any of the groups. In other studies, the antibacterial properties of *C. officinalis* against gram-positive and gram-negative bacteria have been shown.<sup>[49]</sup> This plant has anti-inflammatory, antioxidant, and wound healing properties and has a beneficial effect on the mucosal damage to the vaginal surface,<sup>[50]</sup> which can be a reason for its effectiveness in BV. In the examination carried out by Baig *et al.*,<sup>[27]</sup> *P. integerrima* demonstrated a comparable effect to metronidazole in the management of BV, without any adverse effects. Studies show that *P. integerrima* has antimicrobial, anti-inflammatory, analgesic, and antioxidant activities.<sup>[51]</sup> The therapeutic effect of this plant on BV is likely due to the properties mentioned earlier. In the exploration conducted by Eghbal *et al.*,<sup>[20]</sup> the hydroalcoholic solutions derived from oregano (*Mentha longifolia L.*), peppermint (*Mentha piperata L.*), and summer savory (*Satureja hortensis L.*)



have been compared with metronidazole vaginal gel in the management of BV. The findings indicated that the effect of 5% herbal vaginal cream and metronidazole vaginal gel was effective and similar in reducing complaints and improving Amsel criteria in patients with BV.<sup>[20]</sup> In the study by Leite *et al.*,<sup>[14]</sup> the effect of Brazilian pepper tree (*Schinus*) extract on BV has been investigated. Duration of treatment with Brazilian pepper extract was lower than that of metronidazole gel.<sup>[14]</sup> Mousavi *et al.*<sup>[12]</sup> investigated the effect of propolis gel containing beeswax on BV. They found that there was a significant statistical relationship between the type of treatment and the percentage of improvement of Amsel criteria ( $p < 0.05$ ). The response to treatment in the two groups of metronidazole and propolis was 95.8% and 70.8%, respectively, and the therapeutic effect of propolis on BV was less than metronidazole. Although the response to treatment in the propolis group was lower than that of the metronidazole group, an acceptable percentage of patients recovered.<sup>[12]</sup> The composition of propolis depends on factors such as geographical area, plant origin, and drug preparation and processing technique. Nevertheless, propolis from different geographical regions had similar antimicrobial properties. Despite the fact that they may have different chemical compositions,<sup>[52]</sup> its therapeutic effect can be due to the antimicrobial properties of this substance.

In this review article, we reviewed all the articles that measured the effects of different herbs on BV. Nevertheless, other articles examine the effects of herbs on other types of vaginitis, such as candida or trichomonas vaginitis. For example, in the study by Sarhadinejad *et al.*,<sup>[53,54]</sup> the effect of dill seed vaginal cream on Candidiasis vulvovaginitis was shown, and in treating patients with Candidiasis vulvovaginitis, there was no significant difference between the effectiveness of dill seed vaginal cream and clotrimazole. Fard *et al.*<sup>[55]</sup> investigated the effect of black seed in combination with clotrimazole vaginal gel on candidiasis vaginitis, which had a better effect than clotrimazole vaginal gel alone.

According to the included evidence, other types of vaginitis such as fungal or trichomonas vaginitis were not investigated, and most of the studies were done in Iran, which can limit the results of studies. The strength point of the study was to focus on clinical trial studies that were used to treat patients with BV, which makes it easier to collect a database of complementary therapies in the treatment of vaginitis. It is recommended that future studies review other types of vaginitis such as fungal or trichomonas infections. These studies should compare different herbal medicines to determine which medicinal plant has better efficacy.

## Conclusion

Medicinal herbs are valuable sources for treating various

diseases in herbal medicine practices around the world. Patients and physicians' interest in their use has grown because medicinal plants give them a wider range of options, especially in resistant cases, and they are associated with fewer complications. According to this systematic review, it seems that medicinal plants can play an effective role in reducing the symptoms of BV. Therefore, they can be used as a complementary treatment in BV.

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## Conflicts of interest

Nothing to declare.

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