

## Comparative study of the effects of metronidazole gel and *Berberis vulgaris* gel on the treatment of bacterial vaginosis

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### Abstract

*Berberis vulgaris* has been indicated with various pharmacological properties such as antioxidant and antibacterial effects. Bacterial vaginosis (BV) is the most common infection in women within child bearing ages that creates gynecological problems, pelvic infection, urinary tract infection and malodorous discharge which could lead to infertility, premature birth and miscarriage in women. This study was conducted to compare the effect of metronidazole gel and *B. vulgaris* gel for the treatment and recurrence of BV. This double-blind clinical trial was conducted on 80 women with BV who were referred to women's clinic in Hajar Hospital (southwestern Iran) in 2016 with convenience sampling. The diagnosis criteria were Amsel's criteria, gram staining and culture. The participants were divided in 2 groups. First group received metronidazole gel 0.75 % for 5 nights and the second received *B. vulgaris* gel 5 % for 5 nights vaginally. The symptoms were evaluated for 7 and 21- day follow up. The descriptive and inferential statistics (chi square, t-test and ANOVA) were used to analyze the data using SPSS software. After 7 days of treatment, a significant difference was observed in terms of improving symptoms of irritation, dyspareunia and dysuria in both groups and this level was higher in the group taking *B. vulgaris* gel ( $P < 0.05$ ). The results of a recurrence of symptoms after 21 days of intervention showed that the complete recovery of various symptoms was significantly higher in *B. vulgaris* gel than the metronidazole gel group ( $P=0.001$ ). *B. vulgaris* gel was more effective than metronidazole gel in treating bacterial vaginosis and could be considered as a new therapeutic approach in BV treatment.

**Key words:** Medicinal herbs, sexually transmitted diseases, antifungal drug, *Gardnerella vaginalis*

### Introduction

One of the plants, the different parts of which such as roots, leaves and fruits are used for medicinal purposes is Berberry (*Berberis vulgaris* L.) related to Berberidaceae family (Imanshahidi *et al.*, 2008). *B. vulgaris* L. is a medicinal and edible herb that growing in Europe and Asia. Iran is the biggest producer of *B. vulgaris* fruit in the world, with 11000 hectares of land under cultivation. Over 10000 tons of dried fruits are produced (Rahimi-Madiseh *et al.*, 2017). The plant has obovate leaves, bearing pendulous yellow flowers in spring succeeded by oblong red colored fruits. The fruit, leaf, root and bark have been used in traditional medicine to treat some diseases such as antibacterial, antipyretic, antipruritic and antiarrhythmic activities (Ivanovska and Philipov, 1996; Mokhber-Dezfuli *et al.*, 2014).

Bacterial vaginosis (BV) is a common disease among women that is often developed in the early sexual activity. Since BV is associated with sexually transmitted infection (STI), it is considered as a public health problem (Bautista *et al.*, 2016). The complication in addition to gynecological problems, pelvic infection, urinary tract infection and malodorous discharges could lead to infertility, premature birth and miscarriage in women (van Oostrum *et al.*, 2013; Chawanpaiboon and Pimol, 2010; Kirjavainen *et al.*, 2009). Although BV may have transiently and asymptotically (30 % of BV cases may resolve without treatment), in most cases, cause offensive fishy odor discharge

which reoccurs frequently, often around the time of menstruation (Hay, 2017; Kairys and Garg, 2018). The discharge itself is typically gray or white and thin that can be diagnosed with clinical symptoms and confirmed by obtaining a vaginal swab of the cervical region (Kairys and Garg, 2018). Various factors contribute to development of BV, which include the numerous components of the vaginal microbial ecosystem and their host (Turovskiy *et al.*, 2011). Most microbial agents that cause disease include cocci and coccobacilli such as *Staphylococcus aureus*, *E. coli*, *Gardnerella vaginalis*, *Mycoplasma hominis*, and *Mycoplasma curtisii* (Livengood, 2009; Ghiasi *et al.*, 2016; Hillier, 2005). Among these agents *G. vaginalis* is one of the most important pathogens causing BV which is replaced in vaginal epithelial cells that cause the cells more lubricous (Polatti, 2012; Turovskiy *et al.*, 2011). Therefore, the specific treatments are more based on topical treatments such as using the metronidazole gel and clindamycin cream (Kumar *et al.*, 2011). But the use of synthetic drugs has activated defense mechanisms in bacteria and increases their resistance to microbial agents and this leads to BV recurrence in women (Beigi *et al.*, 2004). Thus the researchers are looking for alternative treatments to deal with microbial resistance to chemical drugs (Kumar *et al.*, 2011).

The use of herbal medicines in the treatment of diseases is increasing due to less complications, easier access and lower cost (Ekor, 2014). Medicinal herbs have shown positive effects on various diseases including vaginal infections (Heidari-Soreshjani

*et al.*, 2017; Memarzadeh *et al.*, 2018; Nikfarjam *et al.*, 2017; Shabanian *et al.*, 2017ab; Shirani *et al.*, 2017; Yavangi *et al.*, 2018). In addition to the numerous medicinal uses, this plant is used in the treatment of viral and bacterial inflammation and infections (Imanshahidi and Hosseinzadeh, 2016). Metronidazole can cause numerous side effects and in some cases the treatment process fails because of microbial resistance (Larsson *et al.*, 2008; Swidsinski *et al.*, 2008; Masoudi *et al.*, 2016).

This study aims to compare the effect of metronidazole and *B. vulgaris* gels alone on the treatment and recurrence of bacterial vaginosis in women.

## Materials and methods

This clinical trial was conducted on women with BV who referred to women's clinic in Hajar Hospital (southwestern Iran) in Feb 2015- July 2016. The sample size was calculated as 70 based on the prevalence and reference to studies (Masoudi *et al.*, 2016) in the field of bacterial vaginosis. In order to enhance the accuracy of the study and consider the loss of sample considered 85 patients and finally 80 patients enrolled. Patients were randomly divided into two groups 40 patients in each that receiving *B. vulgaris* gel and metronidazole gel.

The patients were randomly and alternately divided into two groups by random number table. This study was double blind in which the patients and the physician were unaware of medication.

The inclusion criteria were having three positive criteria of the four Amsel's criteria. Amsel's criteria included factors such as white or gray diluted homogenized vaginal discharge, positive *in vitro* fertilisation (IVF) test, more than 20 % key cells in the vaginal wet smear, pH more than 4.5 (Platz-Christensen *et al.*, 1989), being within the childbearing ages of 18 to 48 and marriage. The exclusion criteria were allergic to *B. vulgaris* L, risk of metabolic and chronic diseases (diabetes, hypertension, kidney disease, thyroid, heart and epilepsy), autoimmune diseases, malignancy, pregnancy, reproductive system abnormalities, menopause, hysterectomy, sperm in fluid sample slides, the use of antibiotics in the last two weeks and creams or vaginal suppositories during the last week, the use of immune suppressants, pelvic infection, spotting, celibacy and alcoholism. Women with vaginosis symptoms were examined by speculum and tested in terms of discharges; their vaginal sample was taken by swabs, the sample was transferred on the slides and Gram stained. The human bilayer twin 80 Human Blood Tween (HBT) was used for *Gardenerella vaginalis* culture.

*B. vulgaris* L fruit, grown in the North East of Iran, was purchased and sun dried and converted into powder after the identification and approval of Herbarium Research Center. For the preparation of alcoholic extract, 100 g of dried fruit powder was mixed with 500 cc of ethanol 80 % and left at room temperature (about 22 °C) for 24 hours. The obtained extract was filtered by paper filter and fed into the rotary (to remove solvent). The resulted alcoholic extract was dried in an incubator at 40 °C. Then 1 g of dry alcoholic extract was added to dimethyl sulfoxide and filtered by millipore syringe with filters with a diameter of 0.22 microns (Haghighati *et al.*, 2003). Finally, vaginal gel of *B. vulgaris* 5 % was prepared.

The first group received Metronidazole gel 0.75 % (purchased

from drug store and produced by Sina Daro Company) for 5 nights and the second group received *B. vulgaris* gel for 5 nights vaginally. After one week, patients were evaluated for response to therapy and the lack of four Amsel's criteria or the presence of only one criterion of Amsel was indicator of the treatment's achievement or failure (Simbar *et al.*, 2003).

Patients who did not improve after seven days of treatment completion were referred for treatment with oral metronidazole. Moreover, complications such as erythema based on PH meter, fever according to clinical examination, and other symptoms including irritation, itching, dysuria, dyspareunia and dysmenorrhea were evaluated based on interviews and talking to the patient and recorded in a checklist designed for this purpose. Also demographic data such as age, age of menarche, age at marriage, education, job, contraceptive methods, number of gravidity, number of parity, number of abortions, history of infection and number of infections during the year were recorded.

Patients were prohibited from sexual intercourse, vaginal washings and taking vaginal medication (like anti-bacterial, anti-fungal and anti-Trichomoniasis drugs). After 5-day treatment period the initial follow up is considered and also three weeks after the treatment the patients were evaluated for recurrence. For recurrence BV 0.75 % metronidazole gel twice weekly for 4-6 months was applied. Patient's treatment compliance was followed up with phone call.

The study was conducted after ethical approval and code (no.28-10-93) provided by the institutional research department in Shahrekord University of Medical Sciences. Patients were enrolled with written informed consent and they were excluded in case of withdrawal from the study. In case of patients' allergy to berberry after applying the gel, they were excluded from the study.

**Statistical analysis:** The data were coded and entered to SPSS v.22 software program. The mean, standard deviation, frequency, percentage and independent t-test, chi square and ANOVA tests were used for statistical analysis. The level of significance was considered as  $P < 0.05$ .

## Results and discussion

Eighty married women with a mean age of 34 years participated in this study. In each group 40 married women who had one partner participated. The majority of the participants had high school diploma and most of them were housewives. Most women used one of the contraception methods among which the natural method was prevalent (Table 1).

Comparing bacterial vaginosis symptoms in different groups at the baseline shows that the two groups did not have significant difference at the baseline and were similar ( $P > 0.05$ ).

There was a significant difference in terms of improving irritation, dispareunia and dysuria symptoms 7 days after the intervention. Although itching, redness, fever and dysmenorrhea were more improved in the *B. vulgaris* gel group than metronidazole group but this difference was not statistically significant (Table 2).

There was a significant difference in terms of improving all symptoms (recurrence of symptoms) including itching, redness, ague, dysmenorrhea, irritation, dispareunia and dysuria in both

Table 1. Comparison demographic characteristics in 2 groups

Variables	Groups	Metronidazole	<i>Berberis vulgaris</i> gel	P-value
Age		33.01±6.41*	32.73±6.98	0.89
Age of menarche		20.25±4.34	20.02±3.8	0.41
Age of marriage		13.45±1.14	13.78±1.07	0.63
Gravidity		2.18±1.31	2.34±1.9	0.37
Parity		2.05±1.30	1.92±1.8	0.15
Abortions		0.53±0.27	0.35±0.63	0.81
Number of infections during the year		4.23±4.3	3.2±4.10	0.6
Education	Illiterate	4	5	0.36
	Elementary	9	4	
	Secondary	9	5	
	High school	10	16	
	Academic	8	10	
Job	Employed	5	7	0.42
	Housewife	35	33	
Contraceptive method	No contraceptive method	4	5	0.84
	Tubectomy	8	6	
	Vasectomy	1	0	
	LD Tablets	2	3	
	Minipills	0	0	
	Condom	5	6	
	IUD	6	5	
	Natural birth control method	13	15	
Infection history	Yes	34	36	0.91
	No	6	4	

\*Mean±SD

Table 2. Comparison of symptom improvement after 7 days in the groups under study

Symptoms	Gropus	Metronidazole		<i>Berberis vulgaris</i> gel		P-value
		Frequency	%	Frequency	%	
Itching	Improved	31	77.5	36	90	0.068
	Slightly better	4	10	4	10	
	Unchanged	5	12.5	0	0	
Redness	Improved	32	80	37	92.5	0.068
	Slightly better	3	7.5	3	7.5	
	Unchanged	5	12.5	0	0	
Ague	Improved	39	97.5	40	100	0.314
	Slightly better	0	0	0	0	
	Unchanged	1	2.5	0	0	
Dysmenorrhea	Improved	33	82.5	38	95	0.103
	Slightly better	3	7.5	2	5	
	Unchanged	7	0	0	0	
Irritation	Improved	27	67.5	39	97.5	0.002*
	Slightly better	7	17.5	1	2.5	
	Unchanged	6	15	0	0	
Disparonia	Improved	32	80	38	95	0.020*
	Slightly better	1	2.5	2	5	
	Unchanged	7	17.5	0	0	
Dysuria	Improved	31	77.5	39	97.5	0.019*
	Slightly better	3	7.5	1	2.5	
	Unchanged	6	15	0	0	

\* Significant difference between the groups under study ( $P < 0.05$ )

groups such that the full recovery of these symptoms was significantly greater in the *Berberis vulgaris* gel than metronidazole group ( $P=0.001$ ) (Table 3).

This study aimed to compare the effect of metronidazole and *B. vulgaris* gel on the treatment and recurrence of bacterial vaginosis. In this study it was found that 7 days after intervention the symptoms *B. vulgaris*

of irritation, disparonia and dysuria were significantly reduced in the group. Also itching, redness, ague, ague and dysmenorrhea were more improved in the *B. vulgaris* gel than metronidazole group, but this difference was not statistically significant. In a study conducted by Massoudi in this area, it was shown that the symptoms of bacterial vaginosis were significantly decreased after applying *B. vulgaris* gel along with metronidazole (Masoudi *et al.*, 2016). In another study that addresses the phytochemistry and pharmacology of *Berberis* species, it was reported that all parts of these plants have antibacterial and anti-malaria effects (Mokhber-Dezfuli *et al.*, 2014). In Masoudi *et al.* study metronidazole-based *Myrtus communis* L and *B. vulgaris* reduced bacterial vaginosis symptoms after seven days (Masoudi *et al.*, 2016). In another study on the antibacterial effects of berberry, kiwi and onion on *Listeria monocytogenes* bacteria it was found that although kiwi extract had a stronger effect on the bacteria, berberry revealed its antimicrobial effects (Anzabi, 2015). Also on the evaluation of berberry seed's hydroalcoholic extract effects against *Staphylococcus aureus* and *E. coli*, it was shown that the simultaneous action of this extract with Cephalosporins can be an effective medicine against *Staphylococcus aureus* and *Escherichia coli* (Shahverdi *et al.*, 2007). In another study it was shown that treatment with the ethanol extract of berberry prevents aflatoxin production in *Aspergillus flavus* and inhibits the growth and proliferation of hepatitis C virus (Ghareeb *et al.*, 2013).

In case of the recurrence of symptoms, the results showed

Table 3. Comparison of symptom improvement after 21 days in the groups under study

Symptoms	Group	Metronidazole (%)	Berberis vulgaris gel (%)	P-value
Itching	Improved	32	80	0.001*
	Slightly better	3	7.5	
	Unchanged	5	12.5	
Redness	Improved	33	82.5	0.001*
	Slightly better	3	7.5	
	Unchanged	4	12	
Ague	Improved	39	97.5	0.001*
	Slightly better	1	2.5	
	Unchanged	0	0	
Dysmenorrhea	Improved	35	87.5	0.001*
	Slightly better	4	10	
	Unchanged	1	2.75	
Irritation	Improved	30	75	0.001*
	Slightly better	6	15	
	Unchanged	4	10	

that 21 days after intervention, all symptoms were significantly decreased in berberry group compared to metronidazole group. In the study conducted by Masoudi *et al.* (2016) no recurrence was observed three weeks after intervention 30 % of patients had recurrence of symptoms in the metronidazole group. The results also showed that women taking metronidazole based *Myrtus communis*. L and *B. vulgaris* compound showed no symptoms of recurrence.

*In vitro* and *in vivo* experiments indicated that *B. vulgaris* and its main phytochemical (berberine) may have anti-diabetic, anti-Alzheimer, anticonvulsant, antidepressant, antioxidant, anti-inflammatory, anti-cancer, antiviral, anti-arrhythmic, antibacterial effects (Mohammadzadeh *et al.*, 2017).

Phytochemical studies indicated the presence of protein, vitamin, alkaloids, lipid, tannins, carotenoid, anthocyanin and ascorbic acid, vitamin K, triterpenoids, phenolic compounds and alkaloids in this plant. The highest amounts of phenolic compounds and anthocyanins can be found in *B. vulgaris* juice and the highest amount of flavonoid compounds in *B. vulgaris* leaves. The flavonols, flavonoids, and phenols of *B. vulgaris* exert antioxidant, anti-inflammatory and antibacterial effects (Rahimi-Madiseh *et al.*, 2016). Studies show that berberry can be effective in the treatment of bacterial and viral infections (Imanshahidi and Hosseinzadeh, 2016) and it is known as an antibacterial agent in traditional medicine. The fruit can be used as a deterrent to *S. aureus* infection (Snowden *et al.*, 2014). One of the active components of berberry is berberine that exists in many Berberidaceae family fruits as an effective ingredient (Ghareeb *et al.*, 2013; Imanshahidi and Hosseinzadeh, 2008). There is still no consensus on the anti-bacterial mechanism of berberry but studies show that berberine is a DNA ligand and is capable of being attached to DNA structure and affect the DNA molecules of the bacteria (Bae *et al.*, 2013; Chi *et al.*, 2014). Another mechanism that has been discussed in this case is inhibition of the cell division protein FtsZ in which berberine could induce its properties (Boberek *et al.*, 2010). Sun *et al.* (1988) reported that berberine sulphate could prevent bacterial adhesion to the epithelial surfaces and mucosa and prevent the formation of fimbrial structure.

Also, berberry as a synergistic agent can be applied with commonly

used antibiotics (Imanshahidi and Hosseinzadeh, 2016). Hence, berberry with its multiple mechanisms can be applied effectively in treating bacterial infections.

In conclusion, *B. vulgaris* gel out performs metronidazole vaginal gel 0.75 % in the treatment of bacterial vaginosis. In addition, treatment with *B. vulgaris* gel prevents the recurrence of the disease. Due to resistance to antibiotics and their complications, berberry can be considered as an appropriate alternative in the treatment of bacterial vaginosis. It is suggested that in future studies, the effect of *B. vulgaris* gel on the treatment of candidiasis and trichomoniasis be investigated.

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