

Original Research Article

In vivo and *in vitro* assessment of hydrogel incorporating *Malva sylvestris* extract for vulvovaginal candidiasis treatment

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Abstract

Purpose: To assess the effect of *Malva sylvestris* (MS) leaf extract incorporated in a hydrogel on vulvovaginal candidiasis.

Methods: The plant leaves were extracted with water and characterized phytochemically. Carbopol 940 was employed as the gel base, triethanolamine as a gelling enhancer, and Nipagin (as preservative) was incorporated into ten hydrogel formulations. The prepared formulations were characterized for pH, viscosity, spreadability, and stability. The selected formula (F6) was selected for *in vivo* assessment of an experimental vulvovaginal candidiasis (VVC) model in three groups of mice, 6 mice each. VVC was induced by intravaginal inoculation, immunosuppressed, and estradiol cypionate was administered subcutaneously to induce the estrus phase. All animals were subsequently inoculated intravaginally. Vaginal load was measured after inoculation to confirm infection at 1, 3, and 6 days as log CFU/mL.

Results: The pH of the developed formulations ranged from 6.65 to 7.1, viscosities ranged from 6000 to 44,000 cP, and spreadability was 26-48 mm. Formulation F6 (Carbopol 940: polyethylene glycol 400 (PEG 400): propylene glycol: Nipagin M sodium: Nipasol M sodium in ratio 1.2: 10: 10: 0.2: 0.1) was selected due to its appropriate characteristics, as its pH was 6.65, spreadability was 46 mm, and its viscosity was 23000 centipoises. It was also assessed *in vivo* and proved significantly more effective compared to miconazole at inhibiting *C. albicans* ($p < 0.05$).

Conclusion: *Malva sylvestris* incorporated into hydrogel with appropriate excipients demonstrated antifungal activity against vulvovaginal candidiasis with a good physicochemical profile.

Keywords: Antifungal, *Candida albicans*, Extraction, Hydrogel formation, *Malva*, Miconazole, VVC

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INTRODUCTION

Plant extracts are a primary source of antioxidant compounds including phenolic acids and flavonoids. These phytochemicals scavenge free radicals and preserve cells from deterioration. Plant extracts are widely employed as beneficial

sources of compounds with antioxidant, antiviral, and antimicrobial characteristics. The emergence of bacterial resistance to conventional antibiotics is considered a significant health challenge, increasing the demand for ongoing research into novel antibiotics that are effective and safe. Plant extracts have received significant attention due

to the proliferation of biologically active compounds being investigated for their effects on bacteria and fungi [1]. Medicinal plants are also a great source of diverse chemical compounds that may be developed into highly selective drugs. The relationship between plant components and their biological efficacy should be known to synthesize compounds with pharmacological activity for various health conditions. The World Health Organization (WHO) has placed significant emphasis on the use of medicinal herbs for global health promotion and advancement of scientific research in this area of interest, particularly in developing countries [2]. *Malva sylvestris* belongs to the Malvaceae family and is recognized as a common mallow in Europe, Iran, and India. It usually grows in wet places such as coastal areas in North Africa, Europe, and Asia. Historically, plant mucilage and flavonoids in leaves and flowers have been utilized to treat various infections and illnesses like colds, burns, coughs, tonsillitis, bronchitis, digestive issues, and eczema [3].

Studies have found that *M. sylvestris* leaf extract contains phenols, flavonoids, terpenoids, catalase enzymes, fatty acids, carotene, and vitamins C and E, which possess anti-inflammatory and antioxidant effects [3]. *Vulvovaginal candidiasis* (VVC) is manifest as vaginal discharge, itching, and erythema. Over 90 % of infections are caused by *C. albicans* [4]. Traditional treatment with vaginal creams, such as Mycozin and clotrimazole, has some problems when used to treat VVC, like allergic reactions resulting in poor compliance. As a result, there has been significant interest in discovering new antifungal natural products [5]. The effectiveness of natural ingredients in topical vaginal products is essential for their therapeutic benefits. For example, organic solvents are often utilized to extract plant materials. They may have poor water solubility and become chemically unstable in specific environments. Therefore, the vehicle or material containing these natural products must be improved upon, making the natural compounds more effective at fighting microorganisms [6]. This study investigated the *in vivo* and *in vitro* antifungal activity of the aqueous extract of *M. sylvestris* incorporated into a hydrogel.

EXPERIMENTAL

Plant sample

Leaves of MS were obtained from Fadak fields, Karbala, Iraq, and authenticated by Dr. Fareed Kabbani at the College of Pharmacy, Al-Zahraa University for Women under number PC015. The

leaves were washed, shade-dried, and ground. The powdered leaves (5 g) were macerated in 30 mL of water for 24 h with intermittent stirring.

The extract was filtered through Whatman filter paper No. 1, and the filtrate was dried employing a vacuum rotary evaporator at 50 °C and stored at 4 °C.

Phytochemical screening

Tannins

The aqueous extract (400 mg) was ultrasonicated for ¼ h at 37 °C with 5 mL of distilled water. After cooling and filtering, 5 drops of 0.1 % ferric chloride (FeCl₃) were added. A blue-black color demonstrated the tannins' presence [7].

Resins

The aqueous extract (400 mg) was combined with 5 mL of distilled water, sonicated for ¼ h, and filtered. Turbidity of the filtrate revealed the resins' presence [7].

Saponins

The aqueous extract (400 mg) was solubilized in 5 mL of distilled water, then ultrasonicated at 70 °C for ¼ h, filtered, cooled, and shaken until a thick continuous foam formed, demonstrating the presence of saponins [7].

Phenols

The aqueous extract (400 mg) was combined with 5 mL of ethanol. The mixture was ultrasonicated for ¼ h and filtered. Thereafter, 2 mL of distilled water and drops of 5 % FeCl₃ were added to the filtrate. A dark green color demonstrated the phenols' presence [7].

Flavonoids

The aqueous extract (200 mg) was mixed with 0.1 mL of 2 % sodium hydroxide solution. A yellow color demonstrated the flavonoids' presence [7].

Quinones

The aqueous extract (400 mg) was sonicated with 5 mL of ethanol at 30 °C for ¼ h. After filtration, 1 mL each of sulfuric acid (H₂SO₄) and the extract was mixed. A red color demonstrated the quinones' presence [7].

Steroids

The extract (400 mg) was ultrasonicated with 5 mL ethanol for ¼ h, then filtered, then evaporated to dryness. A 50 mg portion of the extract was solubilized in 1 mL glacial acetic acid and 1 mL of CHCl₃, then 1 mL sulfuric acid (H₂SO₄) was added through the side of the tube. A green color demonstrated the steroids' presence [7].

Glycosides

The extract (400 mg) was blended with 5 mL of ethanol and ultrasonicated for ¼ h. The mixture was filtered and then evaporated to dryness. Glacial acetic acid (1 mL), 2 % FeCl₃, and H₂SO₄ were used to dissolve the dried extract. Formation of a brown ring demonstrated the glycosides' presence [7].

Terpenoids

The extract (400 mg) was blended with 5 mL of CHCl₃ and ultrasonicated at 30 °C for ¼ h. After filtration, 2 mL of H₂SO₄ was added through the side of the tube. Presence of terpenoids was revealed by a reddish-brown color [7].

Formulation of hydrogel

Triethanolamine (TEA; Sigma Aldrich, USA; 0.1 mL) was added to 60 mL of distilled water containing preservatives to bring the pH to 6.8-7.5 and mixed in a mortar. Different percentages of Carbopol 940 (Sigma Aldrich, USA; 0.3-1.7 %) were incorporated by stirring with a glass rod until a hydrogel formed. In another mortar, 10 g of the extract was levigated with 10 g of propylene glycol (Sigma Aldrich, USA) and 10 g of PEG 400 (Sigma Aldrich, USA). Contents of the two mortars were blended, and the volume was made up to 100 g with water [8] (Table 1).

Characterization of hydrogel

pH analysis

The pH was estimated after dispersing 10 g of *M. sylvestris* aqueous extract hydrogel in 100 mL of distilled water [9].

Viscosity

Viscosity was measured with a viscometer (Brookfield viscometer, USA), spindle 4 speed at 20 rpm [9].

Spreadability

Spreadability of *M. sylvestris* aqueous extract hydrogel was evaluated by measuring the spreading diameter of 1 g of the extract between two horizontal glass slides [9].

In vivo VVC study

A total of 18 female albino mice (body weight 25–30 g, aged 8 – 10 weeks) were gift samples from the Animal House, College of Pharmacy, Al-Zahraa University for Women. The animals were randomly separated into 3 groups, each comprising 6 mice, and were accommodated in stainless steel cages with sipper water bottles. Wood shavings were employed as bedding, replaced every morning, and cages were cleaned and disinfected. The animals were made to acclimatize for 2 weeks with unlimited access to feed and water under standardized conditions (12 h light/12 h dark cycles, 55 % humidity, and 21 °C). Vulvovaginal candidiasis (VVC) was established by infecting female albino mice intravaginally with *C. albicans* ATCC® 10231. A dose of cyclophosphamide (0.1 mg per g) was administered as an immunosuppressant; estradiol cypionate (0.05 mg) was administered subcutaneously once daily for 4 days prior to infection to induce the estrus phase.

Table 1: Formulation table of hydrogel (per 100 g) containing 10 g of MS extract and TEA

Formula	Carbopol 940 (g)	PEG 400 (g)	Propylene glycol (g)	Nipagin M sodium (g)	Nipasol M sodium (g)
F1	0.3	10	10	0.2	0.1
F2	0.6	10	10	0.2	0.1
F3	0.7	10	10	0.2	0.1
F4	0.8	10	10	0.2	0.1
F5	1	10	10	0.2	0.1
F6	1.2	10	10	0.2	0.1
F7	1.4	10	10	0.2	0.1
F8	1.5	10	10	0.2	0.1
F9	1.6	10	10	0.2	0.1
F10	1.7	10	10	0.2	0.1

All mice were subsequently inoculated intravaginally with 0.1 mL *C. albicans* ATCC®

10231 delivered using a micropipette. Vaginal load was measured after inoculation by collecting

vaginal fluid in 0.1 mL sterile saline and quantitative culture on Sabouraud dextrose agar to confirm infection at 1, 3, and 6 days [10]. Colonies that grew at 37 °C were estimated as log CFU/mL [11]. Ethical approval was granted by the Ethical Committee, College of Pharmacy, Al-Zahraa University for Women (approval no. 24, 6 April 2025), and all procedures were performed by adhering to the international guidance for the use of Laboratory Animals [12].

Vaginal topical treatment

The animals were assigned randomly and equally into 3 groups (n = 6 each). Group 1 was infected with *C. albicans* with no treatment. Group 2 was infected with *C. albicans* and treated with miconazole cream 2 %. Group 3 was infected with *C. albicans* and treated with *M. sylvestris* aqueous hydrogel (MS-hydrogel) intravaginally (0.1 mL).

Freeze-thaw cycle

The selected composition (F6) underwent a freeze-thaw cycle. The test was carried out over 12 days with six cycles. In each cycle, the formulation remained at a certain temperature for a whole day (4 °C in the refrigerator and 40 °C in the incubator) [9].

Stability study

The selected formulation gel (F6) packed in aluminum collapsible tubes was subjected to stability investigation at 30 °C / 75 % relative humidity (RH) for a year. Samples were withdrawn after storage and assessed for appearance, pH, viscosity, and spreadability [13].

Statistical analysis

Data were analyzed with IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). The results displayed in log CFU/mL were compared using analysis of variance (ANOVA) with Tukey's post hoc test at $p < 0.05$.

RESULTS

Qualitative test

Findings revealed the presence of tannins, carbohydrates, phenols, flavonoids, and saponins (Table 2).

Table 2: Qualitative tests of *M. sylvestris* aqueous extract

Test	Extract
Tannins	+
Glycosides	-
Phenols	+
Resins	-
Flavonoids	+
Saponins	+
Terpenoids	-
Steroids	-
Quinones	+

Physicochemical properties

All batches were homogeneous in appearance, and their pH ranged from 6.65 to 7.1. Viscosities of formulations F1-F6 were significantly reduced compared to F7 ($p < 0.05$). In contrast, the viscosities of the formulations F8 to F10 were relatively high. Hydrogels produced with a higher amount of Carbopol had viscosities far higher than the requirements stated during the production process. Spreadability was in the range of 26-48 mm, which was affected by viscosity (Table 3).

Table 3: Physicochemical properties of hydrogel formulations

Batch code	pH	Spreadability (mm)	Viscosity (centipoise)
F1	6.85	48	6,000
F2	6.71	45	8,100
F3	6.78	46	10,000
F4	6.84	44	11,500
F5	6.72	43	14,000
F6	6.65	43	23,000
F7	6.86	40	35,000
F8	6.73	31	36,000
F9	6.91	29	40,000
F10	7.10	26	44,000

Antifungal vaginal load

The formula F6 (aqueous MS extract 10 g, Carbopol 1.2 g, PEG 400 10 g, propylene glycol 10 g, Nipagin M sodium 0.2 g, Nipasol M sodium 0.1 g) was shown to have a good physicochemical profile. Hence, it was selected for the *in vivo* study. The vaginal fungal load was assessed in all three groups of animals infected and treated with MS-hydrogel and miconazole compared with the control. The result showed a reduction followed by complete recovery at the end of treatment with MS-hydrogel (Table 5; Figure 1).

Table 4: Vaginal load in all three groups induced with VVC and treated

Group	Day 1		Day 3		Day 6	
	Infected animals (N %)	Log CFU/mL $\pm$ SD	Infected animals (N %)	Log CFU/mL $\pm$ SD	Infected animals (N %)	Log CFU/mL $\pm$ SD
Control	6/6(100)	4.34 $\pm$ 0.29	6/6(100)	4.11 $\pm$ 0.34	6/6(100)	3.76 $\pm$ 0.39
Miconazole cream (20 mg/g)	6/6(100)	3.39 $\pm$ 0.31	5/6(83.3)	1.97 $\pm$ 0.26	0/6(0)	0.0 $\pm$ 0.0
MS hydrogel	6/6(100)	3.34 $\pm$ 0.22	3/6(50)	1.47 $\pm$ 0.57	0/6(0)	0.0 $\pm$ 0.0

CFU/mL (colony-forming unit per mL), SD (Standard deviation)

**Figure 1:** Vaginal loads of *C. albicans* before treatment (A), after treatment with miconazole for six days (B), and after treatment with MS-hydrogel for six days (C)**Table 5:** Stability testing of F6

Item	Before	After	RSD (%)
Appearance	homogeneous	homogeneous	
pH (6-8)	6.65	6.70	0.5
Spreadability (mm)	43	42	1.7
Viscosity (centipoise)	23000	23500	1.5

RSD (Relative standard deviation)

Stability testing

The selected formula F6 was subjected to freeze-thaw cycles and stability testing to investigate changes in physicochemical characteristics, and the results showed no significant changes (RSD < 3 %; Table 5).

DISCUSSION

Qualitative assessment primarily focuses on the presence or absence of secondary metabolites, which are naturally occurring bioactive compounds found in the cells and tissues of medicinal plants. These metabolites are distinguished by their diverse chemical structures and therapeutic properties, which significantly enhance the plant's medicinal value. To achieve this, choosing the most suitable solvent is a priority. The ability of a solvent to effectively extract active phytochemical constituents depends on its polarity, which governs the extent to which bioactive compounds are dissolved and subsequently recovered from the plant material during extraction. Flavonoids are water-soluble constituents; glycosides exhibit antimicrobial characteristics; resins have antiseptic action; and tannins help treat burns, wounds, and disorders of the mucous membranes [14]. The activity of

the extract is due to the many biologically active compounds, including flavonoids, phenols, and tannins [15]. Results of this study revealed that MS comprises a variety of phytochemical compounds, which agrees with prior studies demonstrating that MS aqueous extract contains terpenoids, flavonoids, and phenols [16]. Other main compounds of MS include polysaccharides, coumarins, flavonoids, malvin, malvidin, scopoletin, polyphenols, niacin, folic acid, vitamin A, C, E, and tannins. The pharmacological activity is attributed to multiple components of anthocyanidins, naphthoquinones, flavonoids, and mucilaginous polysaccharides. therefore, the therapeutic effects of the whole plant extract are thought to arise from the combined action of multiple bioactive constituents rather than a single isolated compound [17].

The pH of the formulations ranged from 6.65 to 7.1. The viscosities of formulations F1-F6 were lower than required. On the other hand, formulations F1 - F4 formulated with Carbopol 940 (0.3 to 1 g) did not result in an appropriate viscous hydrogel. However, hydrogels formulated with a significantly higher quantity of Carbopol had viscosities far above the requirements stated during the production process. Spreadability was appropriate (26-48 mm), which was affected by viscosity. The formula F6 (aqueous MS extract

10 g, Carbopol 1.2 g, PEG 400 10 g, propylene glycol 10 g, Nipagin M sodium 0.2 g, Nipasol M sodium 0.1 g) demonstrated the best physicochemical properties; hence, it was subjected to an *in vivo* study using the VVC model. The vaginal fungal load was assessed in all three groups of animals infected and treated with MS-hydrogel and miconazole compared with the control. The findings revealed that the number of colonies decreased significantly following treatment with MS ($p < 0.05$). Furthermore, there was a reduction in the number of colonies followed by complete recovery at the end of treatment with MS-hydrogel, consistent with earlier studies [10].

Numerous studies have explored the effectiveness of plant extracts in treating VVC. For example, Shiravani et al [18] revealed that chamomile extract led to a higher recovery rate in women with *Candida* infections compared to clotrimazole. Additionally, Gaspar de Toledo et al [11] examined the antifungal properties of *Cymbopogon nardus* essential oil in a microemulsion system. The results revealed complete eradication of the infection following treatment against *C. albicans*. In an experimental model for VVC, a vaginal cream comprising curcumin resulted in > 85 % decline in fungal load after 6 days of therapy [17]. Furthermore, Kola-Mustapha et al [19] assessed the antifungal efficacy of essential oils from *Melaleuca alternifolia* and *Cymbopogon flexuosus*, alone and in combination, against *C. albicans*. The emulgel formulae were assessed for their antifungal activity against *C. albicans*. The combined formula containing essential oils was more potent with significant potential for the management of VVC [13].

CONCLUSION

The hydrogel of *Malva sylvestris* (F6) showed appropriate physicochemical characteristics and superior antifungal activity compared to miconazole.

DECLARATIONS

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Ethical approval

Ethical approval was granted by the Ethical Committee, College of Pharmacy, Al-Zahraa

University for Women (approval no. 24, 6 April 2025).

Use of Artificial intelligence/Large language models

We emphasize that no AI tools were employed.

Availability of data and materials

The data used are available from the corresponding author on reasonable request.

Conflict of interest

We confirm that there are no conflicts of interest related to this work.

Contribution of authors

We confirm that the authors named in this article completed the work, and the authors accept full responsibility for any claims related to its content.

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