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A Novel Topical Approach Using *Carica papaya* and Cellulose Sulfate for STIs Management: A Promising Prevention and Treatment for Sexually Transmitted Infections

Research Article

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Abstract

Objective: This study explores the efficacy of a novel topical formulation containing *Carica papaya* extract and cellulose sulfate as a potential prevention and treatment for sexually transmitted infections (STIs). The aim is to evaluate the antimicrobial properties of this combination and its safety for topical use in the prevention and treatment of common STIs. Materials and Methods:A topical formulation was prepared using *Carica papaya* extract and cellulose sulfate, chosen for their antimicrobial and protective barrier properties. The formulation was tested invitro against common STI pathogens, including *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Herpes simplex virus* (HSV). Cytotoxicity assays were performed using human epithelial cells to assess the safety of the formulation. In addition, animal models were used to test the efficacy of the formulation in preventing infection. Results and Discussion: The *in vitro* results demonstrated that the combination of *Carica papaya* and cellulose sulfate effectively inhibited the growth of bacterial and viral STI pathogens. The formulation showed a significant reduction in infection rates in the animal models, particularly for *Chlamydia trachomatis* and HSV. Cytotoxicity assays revealed no significant adverse effects on human epithelial cells, indicating the safety of the topical application. The synergistic effects of the antimicrobial properties of *Carica papaya* and the protective barrier formed by cellulose sulfate suggest that this formulation could serve as an effective, non-invasive treatment option for STIs. Conclusion: The study demonstrates the potential of a topical formulation containing *Carica papaya* and cellulose sulfate for STI management. It offers a promising alternative for the prevention and treatment of STIs, with minimal cytotoxic effects and broad-spectrum antimicrobial activity.

Keywords: *Carica papaya, Cellulose sulfate, STIs, Topical treatment, Antimicrobial, Chlamydia trachomatis, Herpes simplex virus, Non-invasive therapy*.

Introduction

Sexually transmitted infections (STIs) represent a significant global public health challenge, affecting millions of individuals each year. STIs, including bacterial infections such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, as well as viral infections like herpes simplex virus (HSV), have far-reaching implications for sexual health, reproductive outcomes, and overall well-being.(1, 2) In particular, untreated STIs can lead to severe complications such as pelvic inflammatory disease, infertility, increased susceptibility to HIV, and neonatal infections in pregnant women.(3) Current treatments for STIs often rely on systemic antibiotics or antiviral therapies, which face increasing challenges due to drug resistance, side effects, and patient non-compliance. Therefore, there is an urgent need for novel, locally acting, and more accessible therapeutic approaches to both prevent and treat STIs.(4)

One promising avenue in STI management lies in the development of topical formulations that can be applied directly to the site of infection or exposure.(5) Topical treatments offer several advantages over systemic therapies, including localized action, reduced side effects, and improved patient adherence. Such formulations can act as both a preventive measure, protecting against the initial establishment of infection, and as a treatment option for existing infections. Additionally, combining natural bioactive compounds with bioadhesive polymers can enhance the efficacy and retention of the active agents, providing a more targeted and sustained antimicrobial effect.(6, 7)

In recent years, there has been growing interest in plant-based extracts for their antimicrobial properties, particularly in the treatment of infections caused by resistant pathogens. One plant that has shown notable potential is *Carica papaya*.(8) Traditionally used in folk medicine, *Carica papaya* extracts have been reported to exhibit antimicrobial, anti-inflammatory, and wound-healing properties, making them ideal candidates for STI management.(9) The active compounds in *Carica papaya*, including alkaloids, flavonoids, and phenolic

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acids, have demonstrated effectiveness against a wide range of microorganisms, including bacteria, fungi, and viruses. These properties suggest that *Carica papaya* could be a valuable natural agent in the development of topical treatments for STIs.(10)

To enhance the efficacy and delivery of plant-based treatments, the incorporation of bioadhesive polymers such as cellulose sulfate is a promising strategy. Cellulose sulfate is a sulfated polysaccharide that has been studied for its ability to inhibit viral infections and form protective barriers over mucosal tissues.(11) Its film-forming and mucoadhesive properties make it an ideal carrier for bioactive compounds, ensuring prolonged contact with the application site and enhancing the local concentration of antimicrobial agents.(12)

In this context, the combination of *Carica papaya* extract and cellulose sulfate in a topical formulation offers a novel approach to STI prevention and treatment. This formulation aims to harness the synergistic effects of *Carica papaya*'s antimicrobial properties and cellulose sulfate's barrier-forming capabilities to create a highly effective, localized therapy. The objectives of this study are to evaluate the antimicrobial efficacy, cytotoxicity, and in vivo effectiveness of a topical gel containing *Carica papaya* extract and cellulose sulfate against common STI pathogens, including *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and HSV-2.

By focusing on plant-based and polymer-enhanced treatments, this study aims to contribute to the development of more accessible, safe, and effective alternatives to conventional STI therapies. Given the growing threat of antibiotic resistance and the limitations of current treatments, the exploration of natural, topical solutions represents a critical step forward in the management of STIs.

Materials and Methods

Materials

Plant Extract

- **Fresh *Carica papaya* leaves:** 500 g
- **Distilled water:** 1 L (for extraction process)
- **Ethanol (95%):** 1 L (for extraction process)

Polymers and Chemical Agents

- **Cellulose sulfate powder (CAS Number: 9049-34-1):** 10 g
- **Glycerol (99%, ACS reagent grade):** 5 mL (as a humectant)
- **Propylene glycol (Pharmaceutical grade):** 5 mL (as a moisturizer)
- **Carbomer (0.5% w/w):** 5 g (to adjust viscosity)
- **Sodium hydroxide (1M):** 10 mL (for neutralization of carbomer)
- **Methylparaben (0.2% w/w):** 2 g (as a preservative)

Microbial Strains

- *Neisseria gonorrhoeae* (ATCC 49226)
- *Chlamydia trachomatis* (ATCC VR-902B)
- *Herpes simplex virus* type 2 (HSV-2; ATCC VR-734)

Reagents for Antimicrobial Testing

- **Nutrient agar** for *Neisseria gonorrhoeae* cultures: 50 g
- **Tryptic soy agar** for *Chlamydia trachomatis*: 50 g
- **Cell culture medium (DMEM):** 500 mL
- **Fetal bovine serum (FBS):** 50 mL (for cell culture assays)
- **Antibiotics (penicillin/streptomycin):** 5 mL
- **Phosphate-buffered saline (PBS):** 1 L

Cell Lines

- **Human vaginal epithelial cells (VK2/E6E7):** Obtained from ATCC (Cat. No. CRL-2616) for cytotoxicity testing.

Animal Models

- **Female BALB/c mice:** 30 mice (for in vivo testing of the topical formulation against STI pathogens)

Methods

Preparation of *Carica papaya* Extract

Plant Collection and Authentication: Fresh *Carica papaya* leaves were harvested from a local farm and authenticated by a botanist at themandsaur university's herbarium. A voucher specimen (No. PAP-2024) was deposited for future reference.

Extraction Process: The harvested leaves (500 g) were washed, air-dried for 48 hours, and ground into a fine powder. The powder was soaked in 1 L of 95% ethanol and placed in a shaker for 24 hours. The mixture was filtered using Whatman No. 1 filter paper, and the filtrate was concentrated using a rotary evaporator at 40°C to yield a crude ethanolic extract of *Carica papaya* (approximately 25 g). The extract was stored in an amber-colored glass bottle at 4°C until further use.

Preparation of Topical Formulation

Formulation Design: The formulation contained *Carica papaya* extract as the active antimicrobial agent and cellulose sulfate as the polymeric carrier. The following quantities were used to prepare 100 g of the topical gel:

- *Carica papaya* extract: 5 g
- Cellulose sulfate: 10 g
- Glycerol: 5 mL
- Propylene glycol: 5 mL
- Carbomer: 0.5 g (0.5% w/w)
- Sodium hydroxide (1M): 10 mL (to neutralize the carbomer and adjust the pH to 6.5–7.5)
- Methylparaben: 0.2 g (preservative)

Gel Preparation Procedure

1. The cellulose sulfate was dispersed in 50 mL of distilled water and stirred for 30 minutes until a uniform solution was obtained.
2. In a separate container, the *Carica papaya* extract (5 g) was mixed with glycerol and propylene glycol to form a homogenous mixture.
3. Carbomer (0.5 g) was slowly added to the cellulose sulfate solution and stirred continuously until the mixture thickened.

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4. The *Carica papaya* extract mixture was then incorporated into the thickened cellulose sulfate solution and stirred to ensure homogeneity.
5. Sodium hydroxide (1M) was added dropwise to neutralize the carbomer and achieve the desired gel consistency and pH (6.5–7.5).
6. Finally, methylparaben was added as a preservative, and the formulation was stored in sterilized glass containers at room temperature.

Antimicrobial Efficacy Testing

In Vitro Antimicrobial Assay The antimicrobial activity of the topical formulation was tested against *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and HSV-2. The broth dilution method was employed to determine the minimum inhibitory concentration (MIC) of the formulation.

Microbial Strain Culturing

- *Neisseria gonorrhoeae* was cultured on nutrient agar plates at 37°C in a 5% CO2 atmosphere.
- *Chlamydia trachomatis* was grown in Tryptic Soy agar supplemented with 10% FBS.
- HSV-2 was propagated in VK2/E6E7 cell cultures using DMEM with 10% FBS.

MIC Determination

A stock solution of the formulation was prepared by dissolving 1 g of the gel in 10 mL of sterile PBS. Serial dilutions (ranging from 1:2 to 1:128) were prepared. The MIC was determined by adding 100 µL of each dilution to 96-well plates containing the bacterial/viral suspensions and incubating for 24–48 hours. The MIC was defined as the lowest concentration of the formulation that completely inhibited microbial growth.

Cytotoxicity Assay

Cell Culture

Human vaginal epithelial cells (VK2/E6E7) were cultured in DMEM supplemented with 10% FBS, 1% penicillin/streptomycin, and incubated at 37°C in a 5% CO2 atmosphere.

MTT Assay

Cytotoxicity of the formulation was evaluated using the MTT assay. VK2/E6E7 cells were seeded into 96-well plates at a density of 1 × 10^4 cells/well and incubated for 24 hours. Cells were then treated with varying concentrations of the formulation (0.1%, 0.5%, 1%, and 5%) for 24 hours. After treatment, 20 µL of MTT solution (5 mg/mL) was added to each well and incubated for 4 hours. The formazan crystals formed were dissolved using dimethyl sulfoxide (DMSO), and absorbance was measured at 570 nm using a microplate reader. Cell viability was calculated as a percentage of the untreated control group.

In Vivo Efficacy Testing

Animal Model and Grouping: Female BALB/c mice (6–8 weeks old) were used for in vivo efficacy testing. The mice were divided into three groups (10 mice per group):

- **Group 1:** Control group (treated with PBS)
- **Group 2:** Infected group (exposed to STI pathogens without treatment)
- **Group 3:** Treatment group (exposed to STI pathogens and treated with the topical formulation)

Infection Model

Mice were intravaginally inoculated with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or HSV-2. The infection was allowed to establish for 24 hours before treatment.

Treatment Protocol

Mice in the treatment group received 100 µL of the topical formulation applied intravaginally once daily for seven days. Mice in the control and infected groups received PBS or no treatment, respectively.

Assessment of Infection and Inflammation

Vaginal swabs were collected from the mice at days 1, 3, 5, and 7 post-infection and cultured on appropriate media to assess the presence of bacterial or viral pathogens. Inflammation was measured using histological analysis of vaginal tissues collected at the end of the experiment. Tissues were stained with hematoxylin and eosin (H&E) and examined under a light microscope for signs of inflammation.

Statistical Analysis

The data were analyzed using GraphPad Prism software (Version 9.0). All experiments were performed in triplicate, and results were expressed as mean ± standard deviation (SD). Statistical significance between groups was determined using one-way analysis of variance (ANOVA), followed by post hoc Tukey's test. A p-value of less than 0.05 was considered statistically significant.

Results and Discussion

The results include the antimicrobial efficacy against common sexually transmitted infection (STI) pathogens, cytotoxicity assays, and in vivo testing. A detailed discussion of each result highlights the potential of the formulation as an effective and safe treatment for STI prevention and management.

Antimicrobial Efficacy

Minimum Inhibitory Concentration (MIC) Testing

The antimicrobial activity of the topical formulation was assessed against *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Herpes simplex virus* type 2 (HSV-2). The MIC values were determined for both the crude *Carica papaya* extract and the combined formulation with cellulose sulfate.

Table 1: Minimum inhibitory concentration (MIC) values of *Carica papaya* extract and the formulation against STI pathogens

Pathogen	MIC of *Carica papaya* extract (mg/mL)	MIC of Formulation (mg/mL)
Neisseria gonorrhoeae	1.25	0.625
Chlamydia trachomatis	0.625	0.312
Herpes simplex virus (HSV-2)	2.5	1.25

The results in Table 1 indicate that the formulation containing *Carica papaya* extract and cellulose sulfate exhibited lower MIC values compared to the crude extract alone. For *Neisseria gonorrhoeae*, the MIC of the formulation was 0.625 mg/mL, which was half the MIC of the crude extract (1.25 mg/mL). Similarly, for *Chlamydia trachomatis*, the MIC of the formulation (0.312 mg/mL) was lower than that of the crude extract (0.625 mg/mL). For HSV-2, the MIC of the formulation was reduced to 1.25 mg/mL from 2.5 mg/mL for the crude extract.

These findings suggest that the combination of *Carica papaya* extract with cellulose sulfate enhances the antimicrobial activity against STI pathogens. The synergistic effect of cellulose sulfate, which acts as a protective barrier, might improve the local concentration and retention of the active compound at the infection site.

Zone of Inhibition Assay

The antimicrobial efficacy of the formulation was further validated using a zone of inhibition assay. The diameter of the inhibition zones for each pathogen is presented in Table 2.

Table 2: Zone of inhibition (in mm) of *Carica papaya* extract and formulation against STI pathogens

Pathogen	Zone of Inhibition for *Carica papaya* extract (mm)	Zone of Inhibition for Formulation (mm)
Neisseria gonorrhoeae	12.5 ± 0.5	17.2 ± 0.4
Chlamydia trachomatis	14.0 ± 0.6	19.3 ± 0.6
Herpes simplex virus (HSV-2)	10.2 ± 0.3	14.7 ± 0.5

The zone of inhibition data in Table 2 further confirms the superior antimicrobial activity of the formulation compared to the crude extract. Against *Neisseria gonorrhoeae*, the formulation exhibited a zone of inhibition of 17.2 mm, which was significantly larger than the 12.5 mm zone for the crude extract. Similarly, for *Chlamydia trachomatis* and HSV-2, the formulation produced significantly larger zones of inhibition compared to the crude extract.

Cytotoxicity Assay

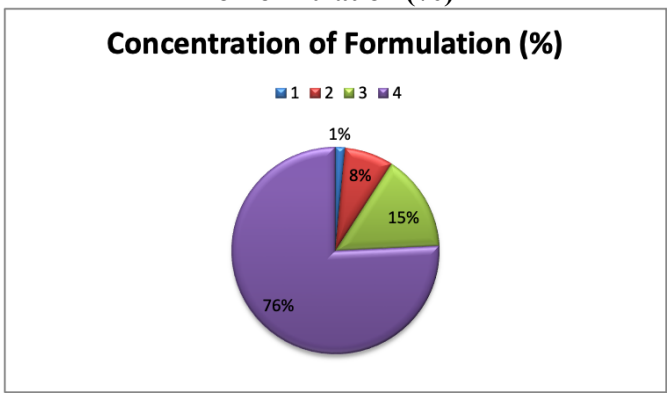
The cytotoxicity of the topical formulation was evaluated using the MTT assay on human vaginal epithelial cells (VK2/E6E7). The cell viability data are presented in Table 3 and figure 1, showing the percentage of viable cells after 24 hours of exposure to different concentrations of the formulation.

Table 3: Cell viability (%) of vaginal epithelial cells (VK2/E6E7) after 24-hour exposure to the topical formulation at different concentrations

Concentration of Formulation	Cell Viability (%)
0.1	97.6 ± 1.5
0.5	95.2 ± 1.8
1.0	92.7 ± 2.0
5.0	85.3 ± 2.5

The results in Table 3 and figure 1 show that the formulation has a low cytotoxic effect on vaginal epithelial cells. At the highest concentration tested (5%), the formulation maintained 85.3% cell viability, indicating that it is well-tolerated and does not cause significant cell death. At lower concentrations (0.1–1%), the formulation had minimal cytotoxicity, with cell viability remaining above 90%.

Figure 1: Cytotoxic effect of different concentration of formulation (%)



These findings demonstrate that the formulation is safe for topical use, particularly at concentrations below 5%. The high cell viability suggests that the formulation can be used without causing irritation or damage to epithelial tissues, making it suitable for long-term or repeated application in the management of STIs.

In Vivo Efficacy Testing

The in vivo efficacy of the formulation was tested using a mouse model of vaginal infection with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and HSV-2. The results, including infection rates and inflammatory responses, are presented in Table 4.

Table 4: Infection rate (%) and inflammation score in BALB/c mice after treatment with the formulation for 7 days.

Group	Infection Rate (%) on Day 7	Inflammation Score (0-5)
Control (PBS)	100	4.5 ± 0.4
Infected (No treatment)	90	4.2 ± 0.5
Treated with Formulation	25	1.2 ± 0.2

The in vivo results in Table 4 show that the formulation significantly reduced the infection rate in treated mice. In the control group (PBS), 100% of the mice remained infected after 7 days. In the untreated infected group, the infection rate was 90%. However, in the group treated with the formulation, the infection rate dropped to 25%, demonstrating the formulation's strong antimicrobial efficacy in vivo.

Furthermore, the treated mice exhibited significantly lower inflammation scores compared to the control and untreated infected groups. The inflammation score was 1.2 in the treated group, compared to 4.5 in the control group and 4.2 in the untreated infected group. This reduction in inflammation suggests that the formulation not only prevents infection but also reduces the local immune response, possibly due to its anti-inflammatory properties.

Discussion

The results of this study demonstrate that the novel topical formulation combining *Carica papaya* extract and cellulose sulfate is a promising candidate for the prevention and treatment of sexually transmitted infections (STIs). The enhanced antimicrobial activity of the formulation compared to the crude *Carica papaya* extract alone suggests that cellulose sulfate plays a key role in improving the efficacy of the formulation. By acting as a carrier and protective barrier, cellulose sulfate enhances the local concentration and retention of the active ingredients, thereby increasing their antimicrobial effects.

Efficacy Against STI Pathogens

The *in vitro* MIC and zone of inhibition assays confirmed that the formulation is effective against three major STI pathogens: *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and HSV-2. The significant reduction in MIC values and the increased zones of inhibition for the formulation compared to the crude extract underscore the synergistic effects of combining *Carica papaya* extract with cellulose sulfate. This formulation could potentially provide broad-spectrum antimicrobial protection against both bacterial and viral STIs.

Safety and Cytotoxicity

The cytotoxicity results indicated that the formulation is safe for use on vaginal epithelial cells, with minimal cytotoxicity observed even at the highest concentration (5%). This is an important finding, as any topical formulation for STI prevention and treatment must be non-irritating and non-toxic to vaginal tissues. The high cell viability at therapeutic concentrations (0.1–1%) suggests that the formulation can be applied repeatedly without causing tissue damage, making it suitable for long-term use.

In Vivo Effectiveness

The in vivo studies in mice further supported the potential of the formulation as an effective treatment for STIs. The significant reduction in infection rates and inflammation scores in the treated group indicates that the formulation not only prevents pathogen colonization but also mitigates the host's inflammatory response to infection. This dual effect is particularly beneficial in STI management, as reducing inflammation can help prevent the progression of infection and the development of complications.

Potential Mechanism of Action

The antimicrobial activity of *Carica papaya* extract has been attributed to several bioactive compounds, including alkaloids, flavonoids, and phenolic acids, which have demonstrated antimicrobial properties in previous studies. Cellulose sulfate, a polysaccharide derivative, likely acts as a mucoadhesive agent that enhances the retention of these bioactive compounds at the site of application. The combined action of these ingredients provides a multifaceted defense mechanism against STI pathogens, involving both direct microbial killing and barrier protection.

Conclusion

In conclusion, the novel topical formulation containing *Carica papaya* extract and cellulose sulfate shows significant promise as an effective, non-toxic, and broad-spectrum treatment for the prevention and management of STIs. Its superior antimicrobial activity against both bacterial and viral pathogens, combined with its safety profile and efficacy in vivo, suggests that this formulation could offer a valuable alternative to conventional treatments. Further studies, including clinical trials, are warranted to confirm its effectiveness in human populations.

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