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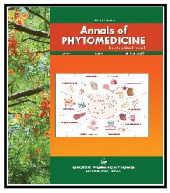

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Biochemical potential of *Cleome viscosa* L.: An investigation into antioxidant, antimicrobial and antibiofilm activities of the methanolic extract against catheter-associated urinary tract infection (CAUTI) causing pathogens

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Abstract

Medical devices are widely used and can impact human health, often leading to severe complications. In particular, catheter-associated urinary tract infections (CAUTI), which are common nosocomial infections caused by biofilm-forming organisms, make treatment challenging. Therefore, there is an urgent need to discover new antimicrobial agents to combat CAUTI infections. Our study investigated the antimicrobial and antibiofilm properties of *Cleome viscosa* L. methanolic extract against *Staphylococcus aureus*, *Candida albicans*, *Escherichia coli*, and *Enterococcus faecalis*. Agar diffusion assays were conducted to confirm the antimicrobial activity. The microdilution method determined the minimum inhibitory concentration (MIC) of *C. viscosa* as 0.5 mg/ml, effectively inhibiting the growth of all tested pathogens. Additionally, biofilm formation inhibition was assessed using crystal violet staining, which showed biofilm inhibition at the MIC level. *C. viscosa* demonstrated a significant reduction in mature biofilms, eliminating 86%, 88%, 83%, and 83% of *S. aureus*, *C. albicans*, *E. faecalis*, and *E. coli* biofilms, respectively. *C. viscosa* coated catheter tubes exhibited antimicrobial effects in an *in vitro* bladder model. Furthermore, the antioxidant properties of *C. viscosa* extract were demonstrated, with no toxic effects observed on normal L929 cells. Overall, the extract shows promising antimicrobial activity and may be considered for CAUTI treatment.

1. Introduction

Urinary tract infections (UTIs) are prevalent across all age groups, ranging from mild cases to severe complications, and pose a significant health concern affecting populations worldwide (Papanikolopoulou *et al*., 2022; Flores-Mireles *et al*., 2015). Previous studies have identified urinary tract infections (UTIs) as the third most common hospital-acquired infection, primarily linked to the use of medical devices (Medina and Castillo-Pino 2019; Skelton-Dudley *et al*., 2019). Generally, the usage of medical devices for life support of admitted patients for longer durations creates vulnerability to infection. Several medical devices can be used for various purposes, urinary catheters play a vital role in draining liquid waste and also, act as the main source of hospitalized infection between patients. More importantly, the urinary catheter allows the external microbes to the sterile urinary tract through the catheter lumen space and attach to the surface of the catheter to form colonization resulting in catheter-associated urinary tract infection (CAUTI) (Feneley *et al*., 2012). Meanwhile, the microbes present in the tract during catheter insertion for an extended period increase the risk for the development of bacteriuria leading to severe complications such as septicaemias, *etc.* (Lo *et al*., 2014). CAUTI is primarily caused by both fungi and bacteria including *Enterococcus faecalis, Candida albicans Staphylococcus aureus*, and *Escherichia coli* are frequently reported organisms in CAUTI (Wooller *et al*., 2018; Kim *et al*., 2017; Saint *et al*., 2016; Sharma *et al*., 2016; Chatterjee *et al*., 2014). These organisms have the ability to form biofilms on both living and non-living surfaces, producing an extracellular matrix that protects the microbes from external stresses and other factors, leading to treatment failure through various evasion mechanisms (Sharma *et al.,* 2016). Biofilms frequently reduce antibiotic susceptibility, contributing to the development of antibiotic-resistant strains, making the treatment of CAUTI highly challenging (Walker *et al.,* 2020; Karigoudar *et al.,* 2019). Therefore, the emergence of antibiotic resistance and ineffective treatments has prompted the exploration of alternative antimicrobial agents for managing CAUTI.

Commonly, during any troublesomeness situation, nature had the solution for all inconveniences. Therefore, many natural sources including marine, plant, and soil have potential pharmaceutical values for the treatment of different dreadful diseases (Arasu *et al*., 2019; Mittal *et al*., 2013). Accordingly, the WHO declared most of the world's population is still relying on traditional medicines for primary health issues (WHO, 2019). However, a huge attraction to phytochemicals from medicinal plants which have effective biomolecules for novel therapeutic applications, and also, the crude plant extract played a vital role during antibiotic overdose as well as towards antibiotic-resistant microbes' emergence rather than individual compounds (Al-Dhabi *et al*., 2019). Hence, *Cleome viscosa* from the Capparidaceae family had ethnomedicinal properties such as anticonvulsant, antimicrobial, wound-healing effects, antidiarrheal,

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anthelmintic, and also used in folk medicine for a longer time (Muhaidat *et al*., 2015). Keeping this evidence, our study examined the methanolic extract of *C. viscosa* antimicrobial activity and antibiofilm activity against CAUTI-causing organisms.

2. Materials and Methods

2.1 Collection and authentication of the plant material

The plant material used in the present study was collected from a local nursery and was identified as *Cleome viscosa* L. by Dr. Mamoon AlFakhi, Chief Scientist, DM Institute of Biological Research, Omdurman, Sudan with authentication number DMIBR/PA/01/2024.

2.2 Preparation of inoculum

S. aureus, E. faecalis, C. albicans, and *E. coli* cultures adjusted to 0.5 MacFarland unit were used and they were grown in mueller hinton broth (MHB), brain heart infusion (BHI) broth, and sabouraud dextrose broth (SDB). The positive controls such as ampicillin, rifampicin nystatin, and methanol were used as vehicle control for the study.

2.3 *C. viscosa* methanolic crude extract preparation

The methanolic crude extract of *C. viscosa* was prepared by placing 20 g of *C. viscosa* powder, obtained from a local market, into a cellulose thimble within a Soxhlet apparatus. Methanol was added as the extraction solvent, and the process continued for several hours until a clear solution was obtained (Harley *et al.,* 2022). The solvent was then evaporated from the crude extract, which was subsequently used for further studies.

2.4 Antimicrobial potential of *C. viscosa* methanolic crude extract

The antimicrobial activity of the *C. viscosa* methanolic crude extract was evaluated against *E. coli*, *C. albicans*, *S. aureus*, and *E. faecalis* using the well diffusion method, as described by Meiyazhagan *et al.* (2016). Two different concentrations of the extract (1 mg and 2 mg per well) were loaded into wells drilled into agar plates inoculated with test pathogens. The plates were then incubated, and zones of inhibited microbial growth around the wells indicated the antimicrobial activity of the extract against the tested pathogens.

2.5 *C. viscosa* methanolic crude extract MIC determination

The minimum inhibitory concentration (MIC) of the *C. viscosa* methanolic crude extract was determined against *E. coli*, *C. albicans*, *S. aureus*, and *E. faecalis* using the microdilution method, as described by Meiyazhagan *et al.* (2015). The extract, starting at a concentration of 4 mg/ml, was serially diluted in the respective broth to a final concentration of 0.031 mg/ml. Cultures of the test organisms were added to each well and incubated for 24 h to allow growth. Subsequently, the optical density (OD) of each well was measured at 600 nm to assess microbial inhibition.

2.6 Effect of *C. viscosa* crude methanolic extract on biofilm formation

The effect of the *C. viscosa* methanolic crude extract on biofilm formation by *E. coli*, *C. albicans*, *S. aureus*, and *E. faecalis* was assessed using the crystal violet method, as described by Meiyazhagan *et al.* (2015). The pathogens were cultured in broth containing serially diluted concentrations of the extract (ranging from 4 mg/ml to 0.031 mg/ml) for five days. The biofilms formed were then fixed with methanol, stained with crystal violet, and treated with an ethanol-acetone mixture. The absorbance of the final product was measured at 570 nm to quantify biofilm formation.

2.7 Mature biofilm eradication capability of *C. viscosa* crude methanolic extract

The effect of the *C. viscosa* methanolic crude extract on mature biofilms of *E. coli*, *C. albicans*, *S. aureus*, and *E. faecalis* was evaluated using the standard crystal violet method (Meiyazhagan *et al.,* 2015). Mature biofilms, grown for five days, were treated with varying concentrations of the extract (1X, 2X, and 3X MIC). Following treatment, the attached biofilms were fixed with methanol and stained with crystal violet. The final product, obtained after adding an ethanol-acetone mixture, was quantified by measuring the absorbance at 570 nm.

2.8 Antimicrobial activity of catheters coated with methanolic crude of *C. viscosa*

The antimicrobial potential of catheters coated with the *C. viscosa* methanolic crude extract was evaluated against *E. coli*, *C. albicans*, *S. aureus*, and *E. faecalis* using an *in vitro* bladder model, as described by Goda *et al.* (2022). Catheter tubes coated with the extract were placed on Petri plates swabbed with overnight cultures of the test pathogens and incubated. Zones of inhibition around the catheter tubes were observed to assess the antimicrobial activity.

2.9 Antioxidant potential of *C. viscosa* methanolic crude extract

The antioxidant property of the *C. viscosa* methanolic crude extract was determined using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay, as previously demonstrated by Gayathri and Sathish Kumar (2016). Briefly, DPPH solution was mixed with various concentrations of the extract (5 mg/ml, 4 mg/ml, 3 mg/ml, 2 mg/ml, 1 mg/ml, and 0.5 mg/ml) and incubated for 30 min. The percentage of free radical scavenging activity was calculated by measuring the absorbance of the final product at 517 nm.

2.10 *C. viscosa* methanolic crude extract cytotoxicity

The cytotoxic effect of the C. viscosa methanolic crude extract was assessed on L929 (mouse fibroblast) cells using the MTT assay, as previously described by Meiyazhagan et al. (2015). The cells were treated with a range of extract concentrations (4 mg/ml, 3 mg/ml, 2 mg/ml, 1 mg/ml, and 0.5 mg/ml). Following treatment, MTT solution was added to facilitate formazan crystal formation, and DMSO was used to dissolve the crystals, producing a purple color, which was measured at 570 nm.

2.11 Statistical analysis

Standard deviations and means were calculated to determine error bars for all experiments.

3. Results

3.1 Antimicrobial potential of *C. viscosa* methanolic crude extract

The antimicrobial activity of the *C. viscosa* crude methanolic extract against *E. coli*, *S. aureus*, *C. albicans*, and *E. faecalis* is shown in Figure 1. As depicted in the figure, two concentrations of the extract tested against the pathogens resulted in zone formation around the wells. A dose-dependent increase in the zone size was observed with higher concentrations of the extract.

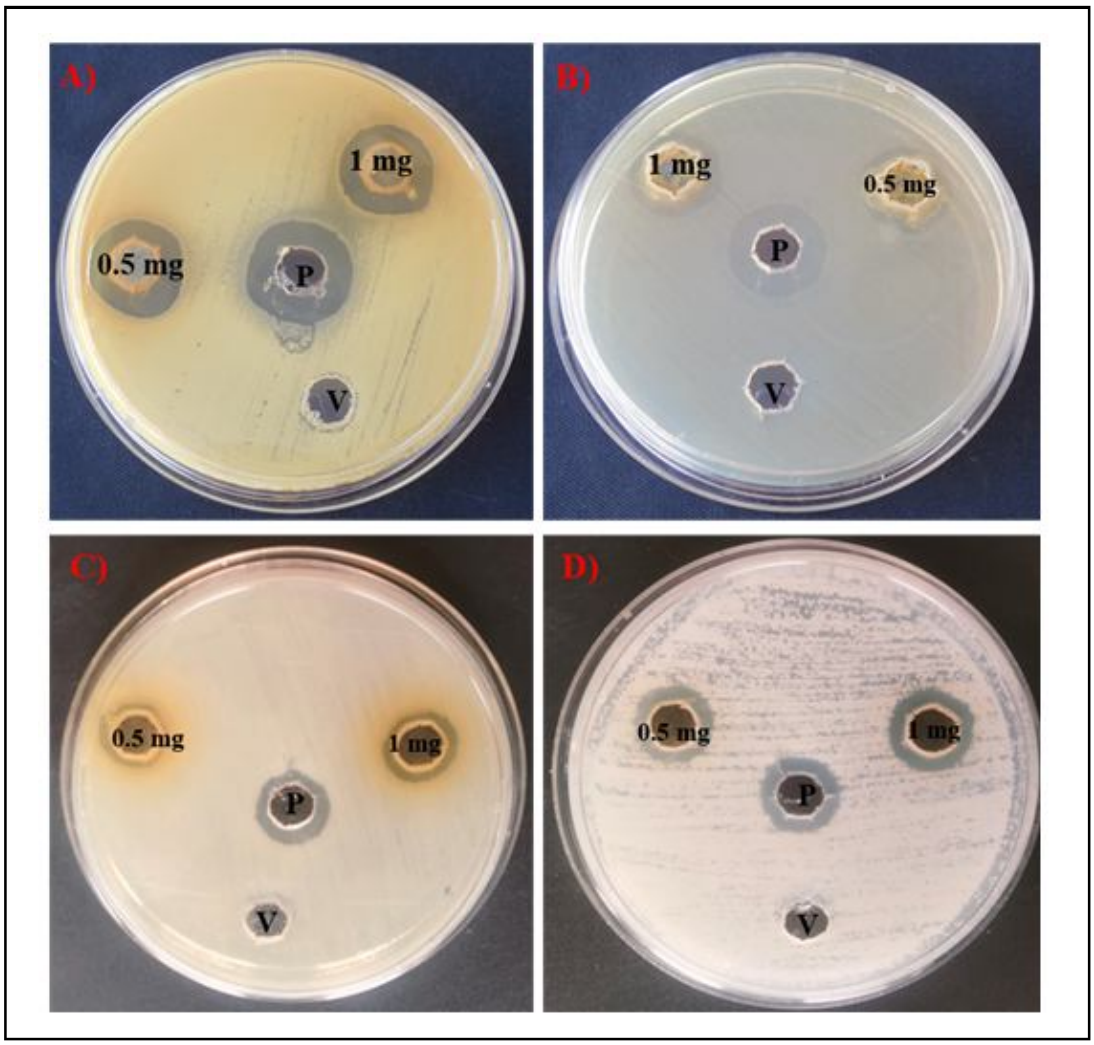

Figure 1: Antimicrobial activity of *C. viscosa* methanolic crude extract (A) *S. aureus* (B) *E. faecalis* (C) *E. coli,* and (D) *C. albicans.* Note: P-positive controls and V-vehicle control.

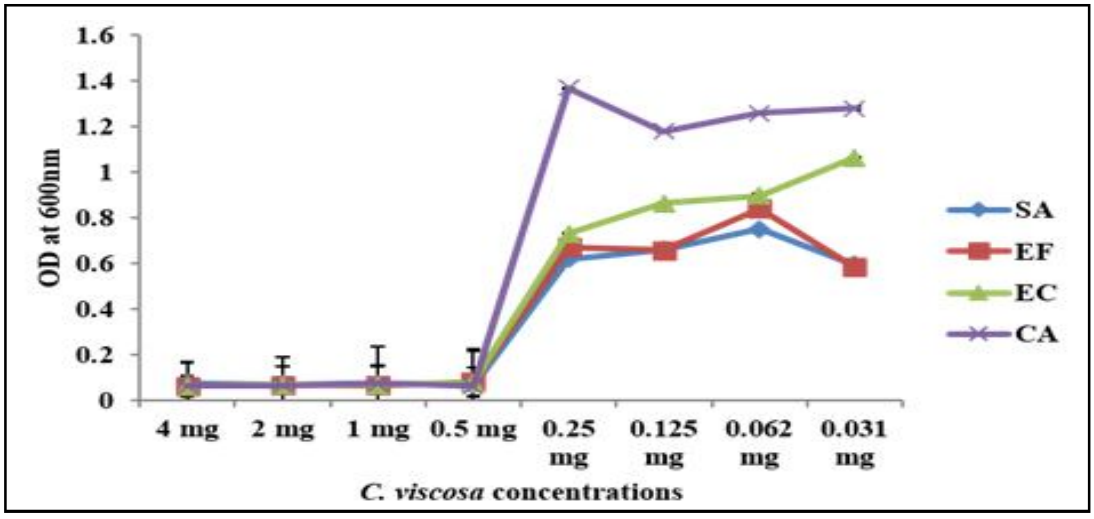

Figure 2: MIC determination of *C. viscosa* methanolic crude extract against *E. coli, S. aureus, C. albicans,* and *E. faecalis* using the microdilution method. Note: SA-*S. aureus,* EF- *E. faecalis,* EC- *E. coli* and CA-*C. albicans.*

3.2 MIC determination for *C. viscosa* crude methanolic extract

The MIC determination of the *C. viscosa* crude methanolic extract against *E. coli*, *C. albicans*, *S. aureus*, and *E. faecalis* was carried out, and the calculated minimal inhibitory concentrations (MIC) are presented in Figure 2. As observed from the figure, a concentration of 0.5 mg/ml of *C. viscosa* methanolic crude extract was sufficient to inhibit the growth of *E. coli*, *S. aureus*, *C. albicans*, and *E. faecalis*.

3.3 Effect of *C. viscosa* crude methanolic extract on biofilm formation

The ability of *E. coli*, *C. albicans*, *S. aureus*, and *E. faecalis* to form biofilms in the presence of *C. viscosa* methanolic crude extract was assessed, and the quantified biofilm formation percentage at various concentrations (4 mg/ml to 0.031 mg/ml) is shown in Figure 3. As observed from the figure, biofilm formation was not detected at the MIC level. However, a gradual increase in biofilm formation was noted above the MICs for all test pathogens. Despite this, overall biofilm formation remained minimal, indicating that small amounts of *C.viscosa* methanolic crude extract effectively reduced biofilm formation.

3.4 *C. viscosa* methanolic crude extract effect on mature biofilm eradication

The ability of *C. viscosa* methanolic crude extract to eradicate *E. coli*, *S. aureus*, *C. albicans*, and *E. faecalis* mature biofilms is quantified and presented in Figure 4. The figure shows the percentage of biofilm eradication achieved with three different concentrations of *C. viscosa* methanolic crude extract (1X, 2X, and 3X MIC). *S. aureus* biofilms were reduced by 76%, 78%, and 86%, while *E. faecalis* biofilms were reduced by 80%, 81%, and 83% at the respective concentrations. Similarly, *E. coli* biofilms were reduced by 78%, 80%, and 83%, and *C. albicans* biofilms were eradicated by 85%, 88%, and 88%, indicating strong antibiofilm activity of *C. viscosa* extract against these test pathogens.

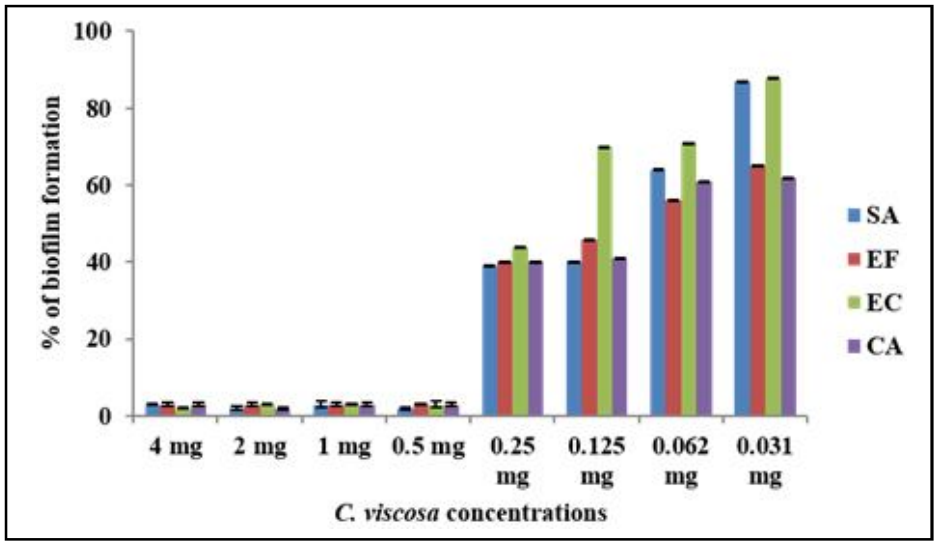

Figure 3: C. viscosa methanolic crude extract impact on the biofilm-forming capacity of *E. coli, S. aureus, C. albicans*, and *E. faecalis*. Note: SA-*S. aureus*, EF- *E. faecalis*, EC- *E. coli* and CA-*C. albicans*.

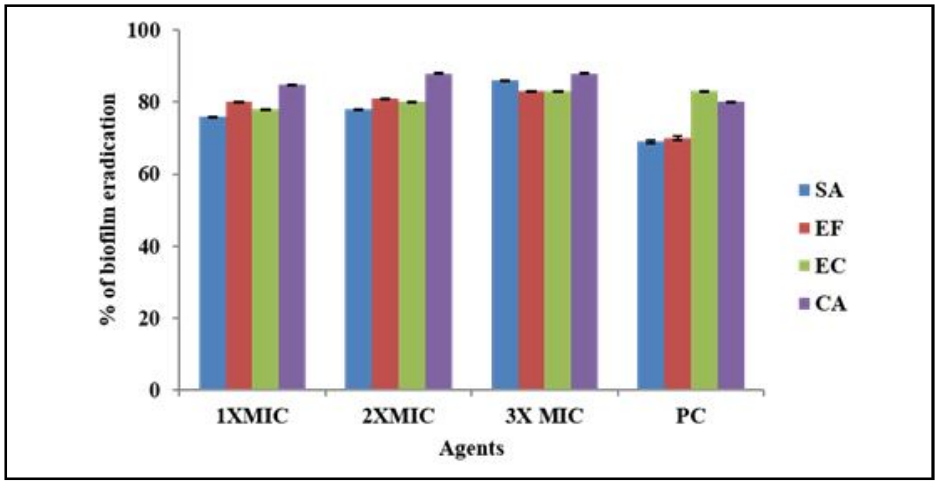

Figure 4: Quantitative analysis of *C. viscosa* methanolic crude extract impact on *E. coli, S. aureus, C. albicans*, and *E. faecalis* mature biofilms. Note: SA-*S. aureus*, EF- *E. faecalis*, EC- *E. coli* and CA-*C. albicans*. PC-positive controls.

3.5 *C. viscosa* methanolic crude extract coated catheter antimicrobial activity

The antimicrobial potential of catheters coated with *C. viscosa* crude methanolic extract was assessed against *E. coli*, *C. albicans*, *S. aureus*, and *E. faecalis* using an *in vitro* bladder model, as shown in Figure 5. The growth inhibition observed around the *C. viscosa* methanolic crude extract-coated catheter demonstrated antimicrobial activity against the test pathogens when compared to the untreated catheter, which showed no zone of inhibition.

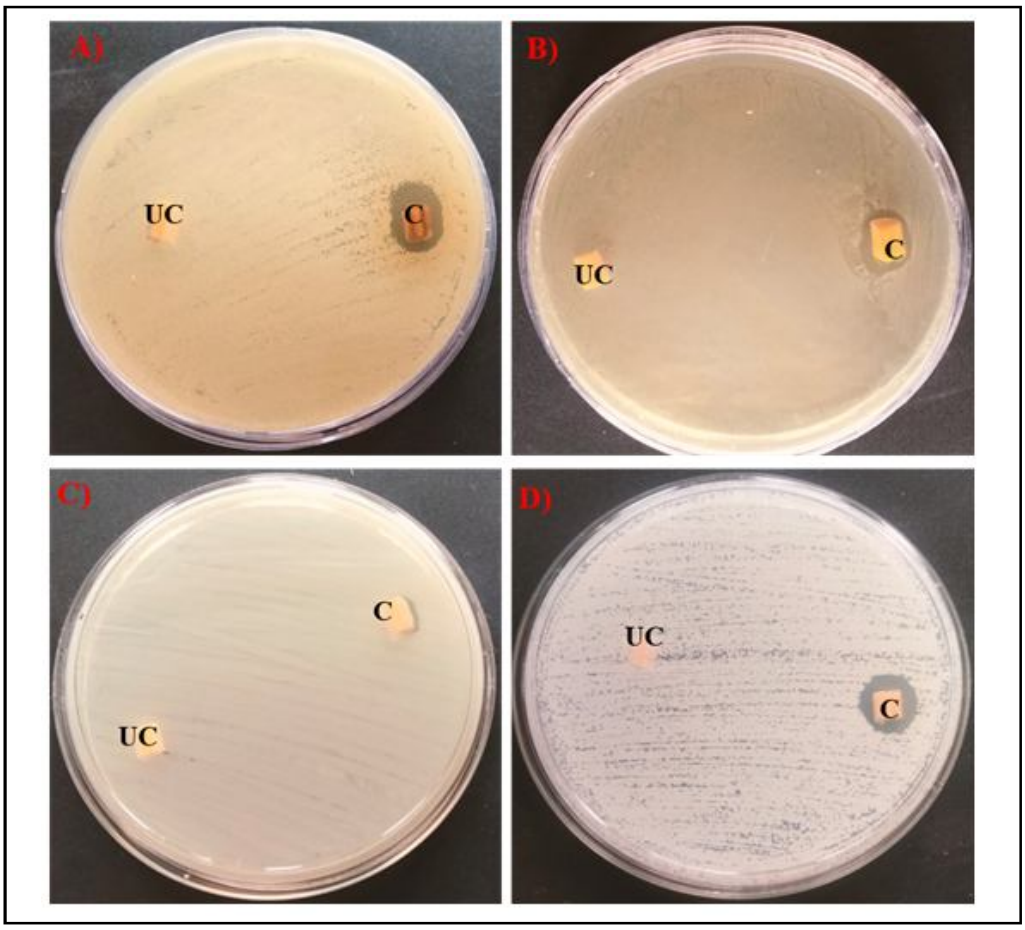

Figure 5: *C. viscosa* methanolic crude extract coated catheter tube antimicrobial activity against *E. coli*, *S. aureus*, *C. albicans*, and *E. faecalis* using *in vitro* bladder model. (A) *S. aureu*, (B) *E. faecalis*, (C) *E. coli*, and (D) *C. albicans*. Note: UC- uncoated, C-coated with *C. viscosa* extract.

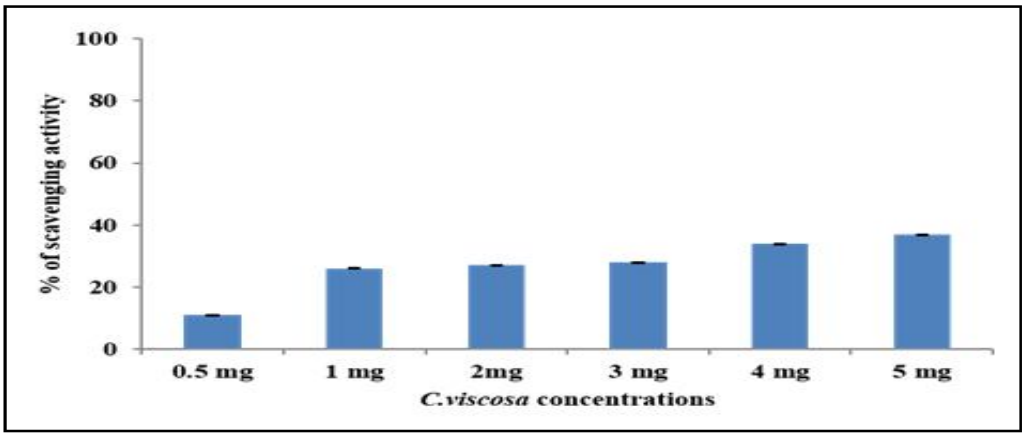

Figure 6: The antioxidant property of *C. viscosa* methanolic crude extract is presented, with the graph depicting the radical scavenging activity of the extract.

3.6 *C. viscosa* methanolic crude extract antioxidant property

The antioxidant property of *C. viscosa* methanolic crude extract evaluated through the DPPH assay is displayed in Figure 6. The free radical scavenging activity of various concentrations (5 mg/ml, 4 mg/ml, 3 mg/ml, 2 mg/ml, 1 mg/ml, and 0.5 mg/ml) of *C. viscosa* methanolic crude extract was found to be 11%, 26%, 27%, 28%, 34%, and 37%, respectively, following treatment.

3.7 Cytotoxicity analysis of crude *C. viscosa* methanolic extract

The cytotoxicity of *C. viscosa* methanolic crude extract was evaluated on L_{929} cells, and the cell viability percentage after treatment is presented in Figure 7. As observed from the figure, *C. viscosa* methanolic crude extract showed no significant cytotoxicity, with the highest cell viability of 96% observed at 0.5 mg/ml, indicating that *C. viscosa* is non-cytotoxic.

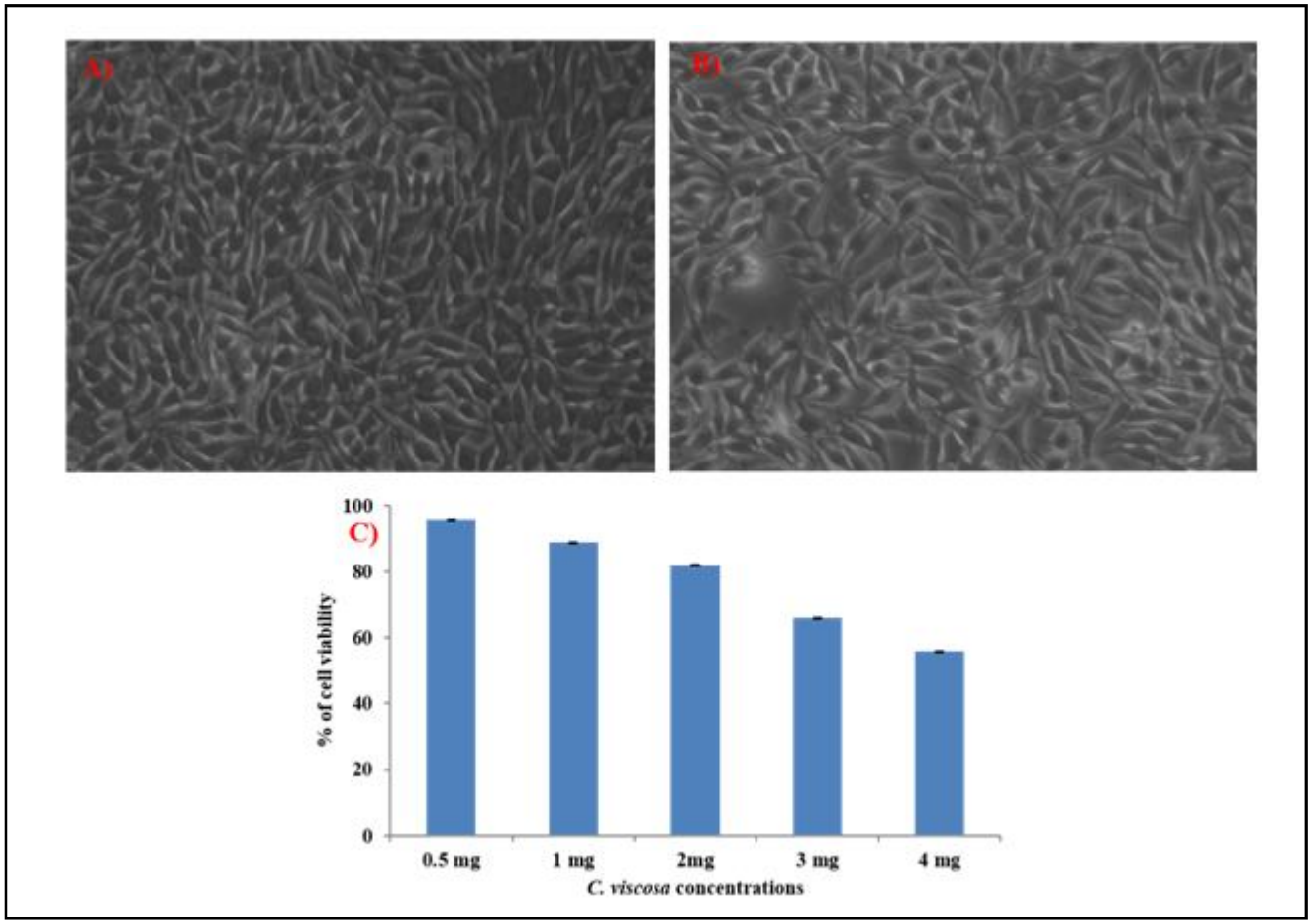

Figure 7: ***C. viscosa*** **methanolic crude extract cytotoxicity on** L_{929} **cells. (A) Untreated cells, (B) Treated with** ***C. viscosa*** **methanolic crude extract, and (C) graph denotes the cell viability percentage after treatment with various concentrations of** ***C. viscosa.***

4. Discussion

CAUTI is a significant nosocomial infection caused by a variety of biofilm-forming organisms which makes treatment harder and critical for physicians resulting in high mortality and morbidity. Generally, CAUTI is a medical device-related infection in the urinary tract due to the use of a catheter for a longer period. The biofilm and resistant development make CAUTI more difficult to treat. Hence, our study examined the methanolic *C. viscosa* extract antimicrobial activity against pathogens involved in CAUTI. The antimicrobial activity of *C. viscosa* was evidenced with the least concentrations for inhibiting the growth of test microbes. In support of this, the bioactive compound imperatorin from *C. viscosa* was isolated and assessed for its antibacterial activity and showed maximum activity at 40 µg/ml concentration against *S. aureus*, *E. coli*, *Klebsiella pneumoniae,* and *B. subtilis*. The study highlighted that the compound can be isolated largely from plants which is easily available across the tropics (Lakshmanan *et al*., 2024). Similarly, the leaf and stem surfaces of *C. viscosa* were extracted with hexane, and their antimicrobial potential was investigated and found the minimal inhibitory concentration was 5 mg/spot and 1mg/spot against *Bacillus subtilis* and *P. fluorescens* respectively. The potent extracted compound diterpene did not inhibit the growth *Cladosporium cucumerinum* (Williams *et al.,* 2003).

Apart from the antimicrobial activity, *C. viscosa* is also explored for its antibiofilm potential against test microorganisms. In the catheterization, the microbial were allowed through the catheter lumen from external sources leading to biofilm formation through various steps such as attachment, colony formation, and maturation which has a complex structure makes treatment challenges for clinicians (Pelling *et al*., 2019; Zhu *et al*., 2019). Consequently, the impression focused on all stages of biofilm formation on non-living surfaces.

Therefore, this study examined the antibiofilm potential of *C. viscosa* methanolic extract against test pathogens by inhibiting biofilm formation and eradicating mature biofilms of the test pathogens, confirming its antibiofilm activity.

Furthermore, the biofilm formation was started through the catheter lumen, therefore, the coating of the catheter's inner and outer surface with methanolic extract of *C. viscosa* is an excellent method for eliminating biofilm on the catheter surface. Hence, our study observed the antimicrobial activity of *C. viscosa*-coated catheter against test pathogens and found the activity by zone formation around the catheter tube. Similarly, numerous studies reported the catheter coating with antimicrobial chemicals like polymer, zinc oxide, some antibiotic combinations, silver and fosfomycin against tested organisms such as *E. faecalis*, *E. coli*, *P. aeruginosa*, *K. pneumoniae* and *C. albicans* (Jia *et al*., 2021; Rahuman *et al*., 2021; Aleksandra *et al*., 2021; Abbott *et al.,* 2020; Fisher *et al*., 2015). Overall, our results recommended *C. viscosa* the methanolic extract excellent antimicrobial and antibiofilm activity *in vitro* to conduct further studies for practical application of coating catheter for CAUTI infection.

5. Conclusion

The methanolic extract of *C. viscosa* antimicrobial activity was evaluated against CAUTI-causing organisms and also showed possible minimal inhibitory concentrations. The *C. viscosa* antibiofilm activity was proved by biofilm inhibition and eradication on non-living surfaces. The *in vitro* bladder model mimicked the suitable microenvironment to show *C. viscosa* extract-coated catheter antimicrobial activity against tested pathogens. Overall, *C. viscosa* extract can be used as an alternative agent for CAUTI infection.

Acknowledgments

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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