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CATHETER-ASSOCIATED URINARY TRACT BIOFILMS: CAN ACHYRANTHES ASPERA EXTRACT WORK AGAINST THEM?

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Abstract

Catheter-associated urinary tract infection is mainly related to biofilm on the catheter surface which provides the opportunity for colonization and attachment resulting complex structured biofilm formation makes development of antibiotic resistant organism creates management of CAUTI is more critical. Therefore, there is an alarming call for drug development against multidrug resistant organisms. Hence, our study attempted the antibacterial activity of methanolic extract of Achyranthes aspera against Staphylococcus aureus one of the prevalent organisms involved in CAUTI. The A. aspera antibacterial activity was determined against S. aureus and minimum inhibitory concentration of A. aspera against S. aureus calculated was as 3.6 mg/ml which needed to inhibit the growth of tested microbe. The colony forming ability of S. aureus was studied in the presence of A. aspera methanolic extract using crystal violet staining method and the colony formation was observed after the MIC level indicates colony formation increases when decreasing the concentration of A. aspera. To ascertain the effect of A. aspera on biofilm formation after treatment with various concentrations, the biofilm formation assay performed. The A. aspera can able to reduce the biofilm formation as 80 and 88% for 1X MIC and 2X MIC against S. aureus indicating the antibiofilm forming ability. To prevent the microbial colonization on catheter surface, the coating of catheter with methanolic extract of A. aspera was investigated for its antibacterial activity against S. aureus using in vitro bladder model. The clear zone formations around the catheter piece indicating the anti-adhesive property of A. aspera against S. aureus. Collectively, methanolic extract of A. aspera can pave the way for new antibacterial agent against S. aureus.

Keywords: *A. aspera*, antibiotic resistance, biofilm, catheter coating, *S. aureus*.

Introduction

The medical devices that are saving the patient life during the admission in the hospital stay. Among the several medical devices are available in the market for public use, the urinary catheter is an important device played a major role in cleaning the urinary system by draining the liquid waste [*Arciola et al., 2018*]. The infections in the urinary system which can able to alter the host defence and the microbiota of the urinary tract leading renal failure [*Skelton-Dudley et al., 2019*]. Accordingly, most of the complicated urinary tract infection occurred when the presence of foreign body such as

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indwelling catheter in the urinary system for liquid waste drainage. Particularly, the catheter usage for prolonged period allowed the bacteria present in urine enter in to the bladder [*Evans et al., 2017; Sikora, 2021*]. This foreign body used for urine drainage from bladder has enough exposure to allow the bacterial entry and colonization on their surface which provides the space for attachment and biofilm development later on [*Regev-Shoshani et al., 2010; Skelton et al., 2019; Singh et al., 2016*]. Generally, the long-term use of catheter may lead to Catheter-associated urinary tract infection (CAUTI) which rank third of very important nosocomial infection occurred during the catheter insertion. CAUTI leads to many complications leading frequent exposure of antibiotic use which makes antibiotic resistant strain development. The antibiotic resistant gained through gene transfer between the biofilm community makes treatment challenges [*Suda et al., 2016; Kang et al., 2015*]. Among the gram positive and gram-negative organisms responsible for CAUTI, *Staphylococcus aureus* was frequently isolated organisms in catheterized patients after receiving the course of antibiotics leading resistant strains development [*Hall and Mah, 2017; Ciofu et al., 2022*]. The frequent or inappropriate use of antibiotic for the treatment option of CAUTI causes the multidrug resistant emergence of isolated organism. The multidrug organism in cauterized patient makes lengthy stay leading high cost and mortality and morbidity rate [*Fotovvati et al., 2019*]. Therefore, the prevention or obstruction of the colonization and biofilm formation of CAUTI causing organism on catheterized surface is needed. Hence, in the study, the antibacterial and anti-adhesive properties of methanolic extract of *A. aspera* were investigated against *S. aureus*.

Since several decades, the products from natural sources gaining much attention due to the wide variety of novel biological compounds with various industrial as well as health importance. Among the others, plant based natural compounds is known for their plenty of rich health benefits such as antimicrobial etc., [*Pieczykolan et al., 2022; Ahmed et al., 2022; Mittal and Dixit, 2013*]. The wide range of antibacterial activity was observed due to the presence of loads of secondary metabolites such as phenolic, flavonoids etc., For these reasons *Achyrantes aspera* was investigated against CAUTI due to their wide spread use in folk medicine. This plant are found in many tropical countries and used for its medical benefits which were investigated for much biological activity [*Dey 2011; Garg and Sardana, 2016*]. Hence, the crude methanolic extract has investigated for their antibacterial, anti-biofilm and anti-adhesive property against *S. aureus*.

Materials And Methods

Preparation of methanolic crude extract of *A. aspera*:

20 g of *weighed A. aspera* powder purchased from local market was dumped into the thimble cellulose tube and placed inside the soxhlet apparatus which used for crude extract preparation as described earlier [*Harley et al., 2022*]. The sufficient methanol volume was added to the flask and the temperature was set at 60^0C to run the cycles for several hours. The extraction procedure was continued till the colourless solvent obtained. The collected crude extract was subjected for solvent evaporation. The obtained product was weighed and used for further analysis.

Antibacterial activity of methanolic crude extract of *A. aspera:*

The *A. aspera* methanolic crude extract was subjected to determine the antibacterial activity against *S. aureus* and *E. coli* as mentioned previously [*Meiyazhagan et al., 2016*]. In short, the prepared sterile MHA plates were swabbed with overnight cultures (0.5 MacFarland units) of above indicated organisms. Then, the plate was allowed to drill the well which receives two concentrations of *A. aspera* crude extract followed by plate incubation. The zone formation around the well indicated the antibacterial activity of *A. aspera* methanolic crude extract against tested organisms. Methanol was used as vehicle control and ampicillin and rifampicin was used as positive controls for *S. aureus* and *E. coli.*

Minimum Inhibitory Concentration (MIC) determination of *A. aspera*:

The *A. aspera* methanolic crude extract MIC was determined against *S. aureus* using micro dilution method as illustrated previously [*Meiyazhagan et al., 2015*]. In brief, the crude extract 3.6 mg/ml added in the MHB containing well was serially

diluted up to 0.02 mg/ml to reach final concentration. The plate was incubated after adding the culture to each well. After incubation, the optical density of the plates was measured at 600 nm. The experiments were done thrice.

***A. aspera* crude extracts effect on colony formation:**

The effect of *A. aspera* methanolic crude extract on *S. aureus* colonization was studied in polystyrene plates as described earlier [*Meiyazhagan et al., 2015*]. For the experiment, the crude extracts effect on *S. aureus* colonization was studied when the extract was serially diluted from (3.6 mg/ml) to reaches the final concentration as (0.02 mg/ml) and the plate was incubated for 96 hours. Later, the attached cells were fixed with methanol after removing the unattached cells by PBS wash. Crystal violet solution (0.1%) was added to stain the fixed cells followed by destained with ethanol acetone mixture. The final purple product was read at 570 nm. The experiment was done in triplicates. The well contain untreated cell served as negative control.

***A. aspera* crude extracts effect on biofilm formation:**

The effect of *A. aspera* methanolic crude extract on *S. aureus* biofilm formation was studied in 12 well polystyrene plates using biofilm formation assay as described earlier [*Gowri et al., 2020*]. In brief, 96 hours of incubation with overnight culture of *S. aureus* in polystyrene surfaces allowed the biofilm formation. The 1X and 2X MIC of crude extract of *A. aspera* was used for the biofilm treatment for 24 hours. Then, the PBS wash removed the unattached cells and attached cells were fixed with methanol. The crystal violet staining was done for fixed cells followed by de staining with mixture of ethanol and acetone. The plates were read at 570 nm and cells without treatment served as negative control. The experiment was done in triplicates.

Antibacterial activity of *A. aspera* coating catheter:

The antibacterial activity of *A. aspera* methanolic crude extract coated catheter against *S. aureus* was investigated in *in vitro* bladder model as described before [*Goda et al., 2022*]. The silicone catheter tube was turned into small pieces and dipped in the crude extract of *A. aspera* and air dry. The sterile MHA plate was swabbed with overnight culture of *S. aureus* and the air-dried piece was placed over the surface. The zone formation around the catheter piece indicates the antibacterial activity of methanolic extract. The experiment repeated twice.

RESULTS

Antibacterial activity of methanolic crude extract of *A. aspera*:

The methanolic extract of *A. aspera* antibacterial activity investigated against *S. aureus* and *E. coli* is presented in figure 1. As noted in figure, the zone formation around the well loaded with various concentration of *A. aspera* indicated the antibacterial activity against the tested organisms. Unfortunately, the antibacterial activity was not observed for *E. coli* up to 10 mg/ml of *A. aspera* (data not shown). But the antibacterial activity was observed in 3.6 mg/ml of *A. aspera* against *S. aureus*. The vehicle control was not showed any zone formation. The zone formation increases when the concentration increases and the *E. coli* were not continued for further studies.

Determination of *A. aspera* Minimum Inhibitory Concentration (MIC):

The MIC of methanolic extract *A. aspera* ascertained against *S. aureus* using micro dilution method and the obtained result is presented in figure 2 and 3. As shown in figure, the graph indicated the lowest concentration of methanolic crude extract of *A. aspera* which needed to inhibit the growth of *S. aureus* calculated was 3.6 mg/ml.

***A. aspera* crude extracts effect on colony formation:**

FIGURE 1: Antibacterial activity of methanolic extract of *A. aspera* against *S. aureus*

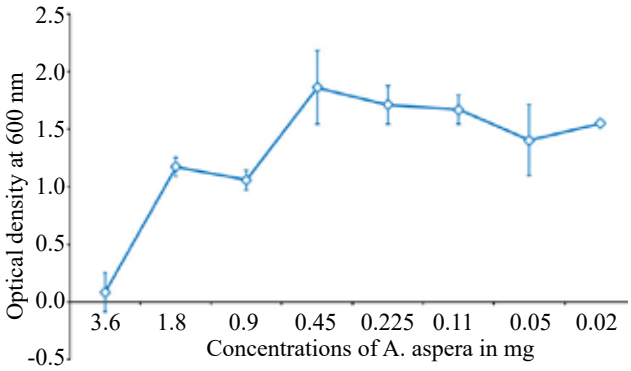

Figure 2: Graph representing the MIC determination of *A. aspera* against *S. aureus*.

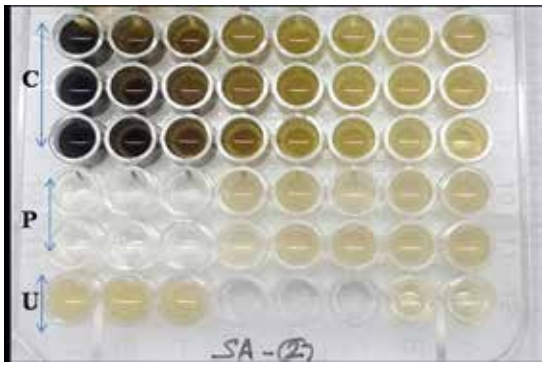

Figure 3: Pictorial representation of MIC determination of *A. aspera* against *S. aureus*.

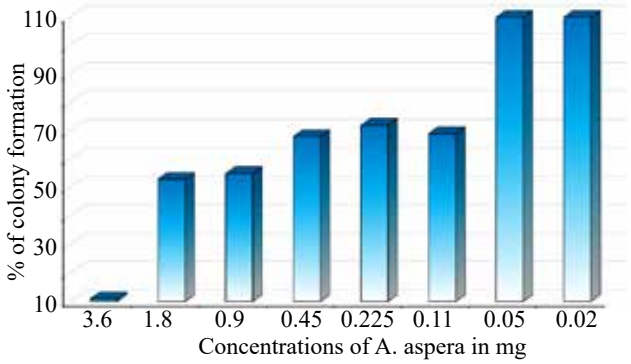

Figure 4: Graph indicating the percentage of colony formation after treatment with *A. aspera* against *S. aureus*

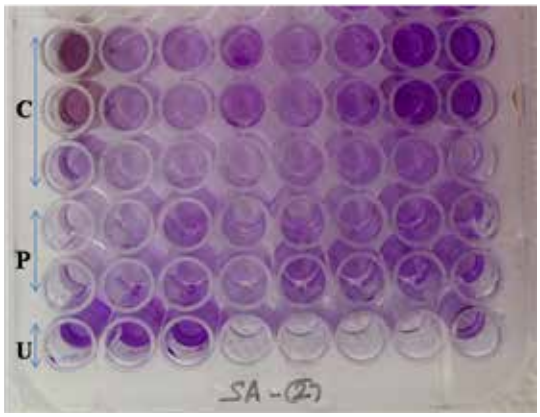

Figure 5: Visual effect of *A. aspera* on *S. aureus* colony formation on polystyrene surfaces

The colony forming ability of *S. aureus* was studied after treatment with various concentrations of methanolic crude extract of *A. aspera* using crystal violet staining method and the percentage of colony forming ability after treatment is represented in figure 4 and 5. As seen in figure, *A. aspera* crude extract was able to inhibit the colony forming ability of *S. aureus* at its MIC level. But the colony forming ability was increased on polystyrene surfaces while decreasing the *A. aspera* methanolic concentration.

***A. aspera* crude extracts effect on biofilm formation:**

The effect of methanolic extract of *A. aspera* was studied against *S. aureus* biofilm formation using biofilm formation assay and the percentage of biofilm formation inhibition quantified using crystal violet staining is presented in figure 6 and 7. As noted in figure, the methanolic extract of *A. aspera* reduces 80 and 88% of the biofilm formation after treated with 1X MIC and 2X MIC concentrations. It showed the ability of *A. aspera* in

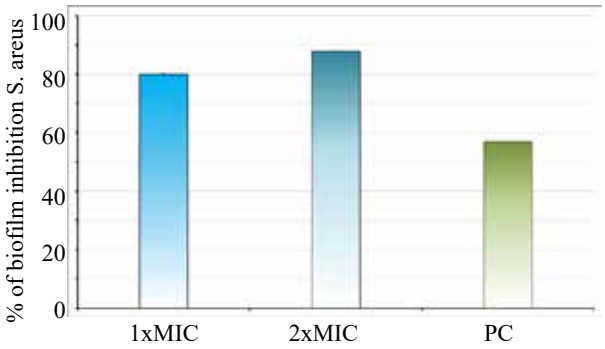

Figure 6: Graph representing the *S. aureus* biofilm inhibition after treatment with *A. aspera*

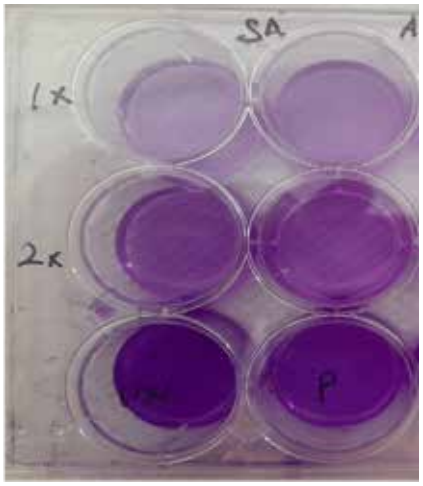

Figure 7: Photographic representation of *S. aureus* biofilm inhibition after treated with *A. aspera*

FIGURE 8: Antibacterial activity of *A. aspera* coating catheter against *S. aureus*

eliminating the biofilm formation formed on the surface of the ploystyrene.

Antibacterial activity of *A. aspera* coating catheter:

The antibacterial activity of catheter coated with methanolic extract of *A. aspera* investigated against *S. aureus* using *in vitro* bladder model and the obtained result is presented in figure 8. As seen in figure, the clear zone formation was observed around the catheter coated piece indicating the antibacterial activity of methanolic extract of *A. aspera* against *S. aureus* thereby the antiadhesive property was proved.

DISCUSSION

Health care associated infection gained much importance due to their mortality and morbidity in the hospitalized patients [*Ansari et al., 2020*]. The incidence of these infections is generally associated with medical devices such as urinary catheters, heart valves and joint prostheses which are used in life saving moment but sometimes it may turned to risk factors. Among the several hospital associated infection, catherter associated urinary tract infection frequently encountered infection leading high economic burden owing to difficult in elimination biofilm formation which makes treatment is more critical [*Jordan et al., 2015*]. The biofilm formation makes antibiotic resistant strains development makes the urgent call for alternative drug development for CAUTI. Therefore, in the study, the methanolic extract of *A. aspera* antibacterial activity was investigated against *S.aureus* and exhibited the potent antibacterial activity and also the inhibitory concentration needed to kill *S. aureus* was 3.6 mg/ml. In support of this, the methanolic extract of *A. aspera* antibacterial activity was investigated against various pathogens including *S. aureus*, *E. coli*, *S. pyogens*, *K. pneumonia* and so on. The result suggested that, *A. aspera* exhibited antibacterial activity against all isolates tested and the least concentration was found to 5 mg/ml [*Nigussie et al., 2021*]. Similarly, the antibacterial activity of various extracts like acetone, methanol and water of *A. aspera* was investigated against various pathogens including gram positive (*S. aureus* and *B. subtilis*), gram negative bacterias (*E. coli* and *K. peumoniae*) and fungi (*C. albicans*) and found the potent antibacterial activity with least inhibitory concentration was below 1 mg/ml. Here, the week antibacterial activity was observed against *E. coli* [*Ndhlala et al., 2015*]. Likewise, *A. aspera* antibacterial activity was observed for *M. tuberculosis* with potent activity [*Beg et al., 2022*]. Another study reported the antibacterial activity of hexane, methanol, ethyl acetate and ethanolic extracts of *A. aspera* was investigated against *S. mutans* causing dental caries and found the good antibacterial activity against tested organism. The least concentration of ethyl acetate extract of *A. aspera* to inhibit the *S. mutans* growth was 0.076mg/ml [*Jebashree et al., 2011; Yadav et al., 2016*].

Besides the antibacterial activity, the methanolic extract of *A. aspera* was investigated for the *S.aureus* colony formation and biofilm formation. CAUTI is mainly associated with biofilm which makes the treatment critical by making antibiotic ineffective through various mechanisms leading development of antibiotic resistant. The uropathogens enter into the bladder through lumen get attached to the surface and colonization leads to biofilm formation very soon. Several stages are needed for biofilm formation like attachment, colonization, think complex polymeric substance produced biofilm formation [*Ghosh et al., 2020*]. So, our aim is to develop novel antibacterial drug agent which have to fight against each stage of biofilm formation. Our study reported the antibacterial activity of methanolic extract of *A. aspera* against *S.aureus* colony formation and found that the extract of *A. aspera* can able to resist the bacterial

growth on polystyrene surfaces indicating the ability of *A. aspera* in eliminating colony formation thereby the biofilm inhibition was proved. The *A. aspera* has the ability to inhibit the biofilm forming ability of *S. aureus*. Further, catheter provides the facility for microbial entry and makes the attachment on the catheter surface resulting severe complication. Therefore, coating of antimicrobial agent on catheter surface is an excellent method to prevent biofilm formation. Hence, the methanolic extract of *A. aspera* was investigated for antibacterial activity after coating the catheter surface against *S.aureu*s and found the excellent antibacterial activity by clear zone formation around the catheter piece. In support of this, the catheter coated with zinc oxide nanoparticle showed excellent activity against *S.aureus* and *E. coli* for seven days [*Aleksandra et al., 2021*]. Similarly, catheter coated with silver nanoparticles antibacterial activity was evaluated against *S. aureus* and *E. coli* [*Rahuman et al., 2021*]. Likewise, antibacterial agent fosfomycin coated catheter showed activity against *E.faecalis* [*Abbott et al., 2020*].

Conclusion

The methanolic extract of *A. aspera* was investigated for their antibacterial activity against *S. aureus* involved in CAUTI. The extract showed antibacterial activity against tested microbe and the least concentration needed to inhibit the growth of *S. aureus* was calculated. The *A. aspera* ability to resist the colony formation was studied after treatment and biofilm reduction was observed. The *A. aspera* coated catheter displayed an excellent activity against *S.aureus* in *in vitro* bladder model. Overall, the methanolic extract of *A. aspera* can be an antibiofilm agent against *S.aureus*.

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