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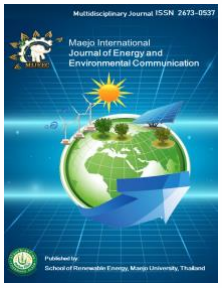

ARTICLE

# A sustainable approach to control biofilms infections and reduce medical waste: Catheters coated with antibiotics inhibit single and dual-species biofilms

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ABSTRACT

Catheter-Associated Urinary Tract Infections (CAUTIs) are one of the major diseases that cause severe illness and death among the wider population. More than 30,000 deaths are reported each year due to CAUTI. These infections are caused due to different biofilm-forming species such as *Escherichia coli* (*E. coli*), *Enterococcus faecalis* (*E. faecalis*), *Candida spp, Klebsiella spp, Proteus spp, Bacteroides spp, Staphylococcus aureus*, and *Enterobacter spp.* This study examined the growth of two major uropathogenic (*E. coli* and *E. faecalis*) strains on catheter surfaces under antibiotic-treated and untreated conditions. The antibiotics used for this study are Ciprofloxacin and Doxycycline, which are considered to be broad-spectrum antibiotics. The Minimum Inhibitory Concentration (MIC) assay was performed to identify the concentration at which these antibiotics show efficient inhibition. The results show that both antibiotics have an inhibitory effect on single and dual-species biofilms. However, *E. coli* is more resistant to Doxycycline (MIC: 100 µg/mL), whereas *E. faecalis* is more resistant to Ciprofloxacin (MIC: 50 µg/mL). Interestingly, the dual-species cultures are more susceptible to both antibiotics at lower concentrations, 5µg/mL. Furthermore, a CFU assay was performed to quantify the results obtained, and a similar trend could be observed with around a 4-fold reduction in bacterial colonies when catheters are coated with antibiotics. In addition, the antibiotic-coated catheters contribute no pathogen contamination to the environment.

## 1. Introduction

This study aims to demonstrate an antimicrobial coating on the urinary catheters could help mitigation of Urinary Tract Infections (UTI) and Hospital Acquired infections (HAI). Both UTI and HAI account for 150 million cases worldwide (Spaulding & Hultgren, 2016). In 2007, the United States of America gathered a statistical

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report on UTIs that shows approximately 13,000 cases recorded annually (Scalise, 2018). Previous studies on UTI have shown that UTI is a serious health issue that leads to death in older men and women of all ages compared to infants (Boyle, 2003). Most UTIs are caused by indwelling catheters, which account for approximately 1 million cases yearly and are medically termed Catheter-Associated Urinary Tract infections (CAUTI) (Cortes-Penfield et al., 2017). It leads to several health complications, such as increased morbidity, mortality, and hospitalization. Compared to other forms of HAIs, CAUTI affects approximately 75% of patients, with an estimated 13,000 fatalities annually (Marissa et al., 2021). In general, biofilm-associated CAUTI is polymicrobial. Uropathogens such as *Escherichia coli* (*E. coli*) (23.9%), *Candida* spp (17.8%), *Enterococcus faecalis* (*E. faecalis*) (13.8%), *Pseudomonas aeruginosa* (*P. aeruginosa*) (10.3%) were the significant contributors for CAUTI (Govindarajan & Kandaswamy, 2022; Govindarajan, Viswalingam, Meganathan, & Kandaswamy, 2020; La Bella et al., 2021; Shanmugasundarasamy, Govindarajan, & Kandaswamy, 2022). In addition to catheters, biofilms infections were also associated with other implants, such as human cochlear implants (Pawlowski et al., 2005), orthopedic implants (Wickramasinghe et al., 2018), endosteal implants (Myllymaa et al., 2013), hernia surgical mesh implant (Rastegarpour et al., 2016), spinal implants (Warburton et al., 2020), breast implants (Verhorstertet al., 2020), and pelvic organ prolapse (Diedrich et al., 2023). Therefore, it is essential to develop a biofilm model system is essential to evaluate biofilm formation's efficacy and antimicrobials' effect on catheters.

Antimicrobial coating on the catheter has attracted much attention for its effective reduction of biofilms in indwelling catheters (Guiton et al., 2010). In addition, rodent models include inoculating bacterial species via transurethral into the bladders of healthy or streptozocin-induced diabetic mice (Guiton et al., 2010; Letica-Kriegel et al., 2019). This model has been proven effective in studying *E. faecalis*-mediated pyelonephritis (Rosen et al., 2008). Catheters doped with nanoparticles have become very effective due to their bioavailability property, such as high stability and lower solubility (Mudshinge et al., 2011). Previous studies have shown that silver nanoparticles (AgNPs) -coated to plastic catheter resulted in reduced biofilm formation and inhibited uropathogens such as *E. coli*, *Enterococcus spp.*, *S. aureus*, *P. aeruginosa*, coagulase-negative *Staphylococci spp.*, and *Candida albicans* (Roe et al., 2008). In addition, AgNPs-coated catheters demonstrated in mice studies did not cause inflammation or toxicity (Roe et al., 2008). An earlier study (Pickard et al., 2012) showed that zinc (Zn) - doped copper oxide nanoparticles were coated on the urinary catheters, which reduces biofilm formation of about 90 % of in various pathogens such as *Enterococcus spp.*, *S. aureus*, *P. aeruginosa*, coagulase-negative *Staphylococci*, and *Candida albicans* (Shalom et al., 2017). Silver ions and AgNPs have been widely used in all metal-based coating. However, clinical investigations have yielded inconsistent results. Copper nanoparticles, in combination with Zn and AgNPs, demonstrated significant antibacterial activity (Marissa J Andersen & Flores-Mireles, 2019). Similarly, Nitrofurazone coated catheters prevent biofilm formation but cause discomfort in patients and are carcinogenic to humans (Schumm & Lam, 2008; Zhu et al., 2019). In addition, AgNPs, and ZnNPs, were synthesized from various biological sources have shown promising results in the mitigation of uropathogenic strains (Govindarajan et al., 2023; Ramya et al., 2019; Sivaramakrishnan et al., 2019), which indicates their limited usage in catheter coating applications.

A recent finding has shown that extracellular iron plays a significant role in bacterial colonization, formation of biofilms, and increased antibiotic resistance in bacterial strains such as *Vibrio cholerae* (*V. cholera*) (Gómez-Garzón & Payne, 2020), *E. faecalis* (Govindarajan et al., 2022), and others ions such as copper and zinc promote the growth of algal species such as *Spirulina plantensis* signifies it contains ion acquisitions systems (Kaushik et al., 2022; Palanisamy et al., 2023). Previous studies have shown that ferrous iron transporter proteins (Feo) acquire extracellular iron, promote redox reactions in the bacterial cells, and release electrons, boosting certain bacterial functions. For instance, the *V. cholerae* FeoB (VcFeoB) system exhibits ATP/GTP hydrolysis, which increases iron uptake, and both FeoA and FeoC are responsible for Feo-mediated iron transport. FeoB requires an energizing source, such as FeoAC, to regulate its function (Gómez-Garzón & Payne, 2020). However, the contribution of individual Feo proteins remains unclear for other species, such as *E. coli* and *E. faecalis.* UTI and CAUTI infections were attributed to several bacterial virulence proteins, such as pili/fimbriae, that facilitates host-pathogen interaction and attachment to the catheter surfaces (Govindarajan & Kandaswamy, 2022; Govindarajan et al., 2020; Shanmugasundarasamy et al., 2022). Also, several fluorescent-based techniques have emerged to identify the localization of proteins, antibiotics, and small molecules in bacterial cells (Meganathan, 2024). Therefore, this study reports the effect of antimicrobial coating on urinary catheters. In addition, this study also evaluates the inhibitory effect of two broad-spectrum antibiotics (Ciprofloxacin and Doxycycline) on single and dual-species biofilms formed on urinary catheters.

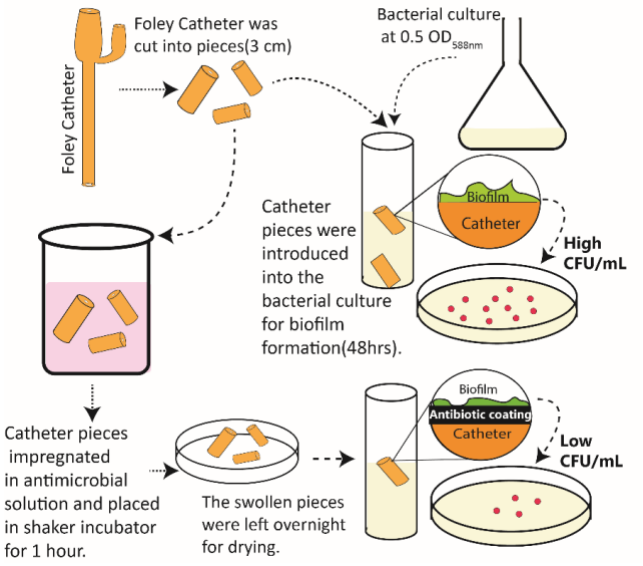


**Figure 1.** Procedure to coat antibiotics on catheters.

The coating approach used in this study has a better turn-around time, as we can assess the efficacy of any antimicrobial in a few days as opposed to mouse model experiments, which usually take several months. Although there were several studies conducted using catheters, those studies either use nanoparticles or Nitrofurazone, and those compounds are either toxic or mutagenic. (Guiton et al., 2010; Rosen et al., 2008). This study demonstrates the application of wide-spectrum antibiotics such as ciprofloxacin and doxycycline in coating with urinary catheters to reduce the formation of biofilm and inhibit bacterial colonization. Doxycycline and ciprofloxacin were used in this

study due to their biological activity, as they inhibit protein synthesis by binding to the 30 S subunit of the Ribosome, thereby stalling the translation of mRNA in bacterial pathogens. Our result showed a significant reduction in *E. faecalis, E. coli,* and dual-species biofilms formation at 100µg/mL of ciprofloxacin coating on the catheters. Catheters coated with 100µg/mL of ciprofloxacin reduce the *E. faecalis, E. coli,* and dual-species biofilms by 74 %, 35 %, and 54 %, respectively. Similarly, 200 µg/mL of doxycycline coating on the catheters reduce the *E. coli, E. faecalis,* and dual-species biofilms by 68 %, 61 %, and 63, respectively. In essence, this study could serve as a test bed to evaluate the antimicrobial effect of any compounds that can be coated on medical implants. Our study shows 100µg/mL of ciprofloxacin coating on the catheters reduces the *E. coli, E. faecalis,* and dual-species.

## 2. Material and methods

### *2.1 Bacterial strains and culture methods*

Bacterial strains were cultured using the method described in earlier studies (Govindarajan et al., 2022). Gram-positive (*E. faecalis*: OG1RF) and Gram-negative (*E. coli*: MTCC 443) bacterial strains are used in this study. The bacterial strains are grown in Luria-Bertani (LB) media throughout the assay (HiMedia). The bacterial strains are streaked on the agar plates and incubated overnight at 37 °C. After incubation, the single bacterial colonies were isolated and transferred to LB broth as a subculture. Overnight cultures were freshly prepared for every assay and performed under sterile conditions. Other materials such as Foley's catheters (Teleflex Medical Private Limited), 15 mL centrifuge tubes (Tarsons) and petri dish (Himedia), 1X Phosphate Buffer Saline (PBS) (sodium chloride (0.137 M), potassium chloride (0.0027 M), sodium Phosphate Dibasic (0.01 M), and Potassium Phosphate Monobasic (0.0018 M), and 100 mL of $H_2O$, optimized the pH to 7.4) were freshly prepared and autoclaved for all the assay. Antibiotics such as Ciprofloxacin and Doxycycline were prepared at a concentration of 1 mg/ml and diluted to lower concentrations such as 100, 50, 25, 10, and 5 µg/mL for MIC assay.

### *2.2 Preparation of single and dual-species bacterial cultures*

Five microliters of overnight *E. coli* and *E. faecalis* bacterial cultures were pipetted to two different 50 mL LB broths and incubated at 37 °C and 90 rpm. The OD of the bacterial cells was recorded every 20 mins in UV-Vis spectrophotometry at $OD_{588nm}$. Upon obtaining an OD value of 0.5, equal volumes (1 mL) of *E. coli* and *E. faecalis* were then pipetted to the fresh test tube to make a dual-species bacterial culture, and the same was used for all assays (Govindarajan et al., 2022). All the experiments were done in biological triplicates.

### *2.3 Biofilm assay using catheters*

One mL of overnight culture (*E. coli, E. faecalis*, and dual-species) is sub-cultured into 100 mL LB broth and incubated at 37 °C and 90 rpm until it reaches 0.5 $OD_{588nm}$. A 5 µL of bacterial cultures was transferred to 5 mL of fresh LB broth in 15 mL tubes (Govindarajan et al., 2022). Then, sterile catheters were chopped into several pieces at a length of 3 cm, and one piece was transferred to the 15 mL tubes containing 5 mL LB broth and inoculum. The tubes were incubated at 37 °C without shaking for 48 h. All the experiments were done in biological triplicates.

### *2.4 Minimum Inhibitory Concentration Assay*

The MIC assay is experimented with to identify the lowest concentration of antimicrobials required to inhibit the bacteria (Govindarajan et al., et al. (2022)). Top Layer Agar (TLA) plates were prepared to perform the MIC assay. The bottom layer of TLA plates contains 1.2 %, LB Agar. The top layer contains 5 mL bacterial cultures (*E. coli, E. faecalis,* and dual-species selected at 0.5 OD at 588 nm) mixed with 20 mL of LB soft agar (0.8% agar) at 45°C and poured into plates. The antibiotics, such as ciprofloxacin and doxycycline, were prepared at varied concentrations such as 5, 10, 25, 50, 100, 150, and 200 µg/mL. About 5 µl of the antibiotic sample was pipetted from the working concentration to Petri dishes. The plates were then incubated overnight at 37ºC. After incubation, a visible circular region called the "zone of inhibition" was recorded (Govindarajan et al., 2022). All the experiments were done in biological triplicates.

### *2.5 Antimicrobial coating on the catheter*

Antimicrobial coating on catheters was experimented with as described in previous studies (Al-Qahtani et al., 2019). The MIC results show that doxycycline concentrations such as 100 and 50 µg/mL inhibit *E. coli* cultures. While 100, 50, 25, 10, and 5 µg/mL of doxycycline inhibit *E. faecalis* cultures, 100, 50, 25, 10, and 5 µg/mL of doxycycline inhibits dual-species cultures. Secondly, ciprofloxacin concentrations such as 100, 50, 25, 10, and 5 µg/mL inhibit *E. coli* cultures, 100µg/mL of ciprofloxacin inhibits *E. faecalis* cultures, and 100, 50, 25, 10, and 5 µg/mL of ciprofloxacin inhibits dual-species cultures. The results showed that the MIC of doxycycline was 50, 5, and 5 µg/mL to *E. coli, E. faecalis,* and dual-species, respectively. Similarly, the MIC of ciprofloxacin was 5, 100, and 5 µg/mL to *E. coli, E. faecalis,* and dual-species, respectively.

Then, the 3 cm catheter pieces were immersed into ciprofloxacin and doxycycline solutions and incubated at a 37 °C shaker incubator for 1 h. Then, the catheter pieces were allowed to air dry for 8 h at room temperature. Once dried, the catheter pieces were transferred to the 15 mL tubes containing 5 mL LB broth and inoculum and allowed to incubate at 37 °C without shaking for 48 h. All the experiments were done in biological triplicates (Al-Qahtani et al., 2019). (Figure.1).

### *2.6 Estimation of biofilm formation on catheters*

The catheters (antibiotic-treated and control (untreated) in 15 mL culture tubes were gently removed after 48h and transferred to a tube containing 5 mL of 1X PBS solution. Then, the tubes were vortexed thoroughly to remove the biofilms from the catheter surfaces. The biofilm volume in the PBS solution was estimated in UV-Vis spectrophotometry at $OD_{588nm,}$ and the values were tabulated to estimate the % inhibition of biofilms. In addition, the biofilm cultures were serially diluted using 1x PBS solution and 5 µL of the serially diluted cultures were plated on the LB agar plates to estimate the colony-forming units (CFU/mL).

$$CFU/mL = \frac{No.of\ colonies * dilution\ factor}{Volume\ plated}$$

### *2.7. Statistical analysis*

All statistical analyses were performed using GraphPad Prism 8.0.1. Statistical significance was determined by unpaired t-test for column-wise comparison. n=3 (biological replicates). **** indicate P≤0.0001, *** indicate P≤0.001, ** indicate P≤0.01, and * indicate P≤0.05 (Govindarajan et al., 2022).

## 3. Result and Discussion

### 3.*1 E. coli* and *E. faecalis* are more resistant to doxycycline and ciprofloxacin, respectively

Firstly, antibiotic inhibition results (figure.2) show that doxycycline concentrations such as 100 and 50 µg/mL inhibit *E. coli* cultures. While 100, 50, 25, 10, and 5 µg/mL inhibit *E. faecalis* cultures, 100, 50, 25, 10, and 5 µg/mL inhibit dual-species cultures. Secondly, ciprofloxacin concentrations such as 100, 50, 25, 10, and 5 µg/mL inhibit *E. coli* cultures, 100µg/mL inhibits *E. faecalis* cultures, and 100, 50, 25, 10, and 5 µg/mL inhibits dual-species cultures. The results showed that the MIC of doxycycline was 50, 5, and 5 µg/mL to *E. coli*, *E. faecalis*, and dual-species, respectively. Similarly, the MIC of ciprofloxacin was 5, 100, and 5 µg/mL to *E. coli*, *E. faecalis*, and dual-species, respectively. (Figure.2)

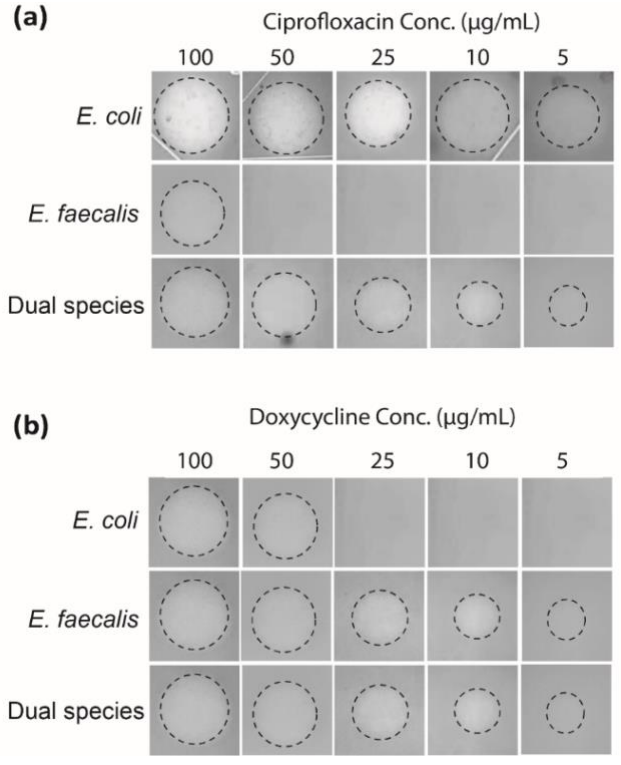


**Figure 2.** Minimal Inhibitory Concentration of doxycycline and ciprofloxacin. (a) the MIC of doxycycline was 50, 5, and 5 µg/mL to *E. coli*, *E. faecalis*, and dual-species, respectively. (b) Similarly, the MIC of ciprofloxacin was 5, 100, and 5 µg/mL to *E. coli*, *E. faecalis*, and dual-species, respectively.

### *3.2 Ciprofloxacin and doxycycline coating to the catheters significantly reduces the biofilm formation*

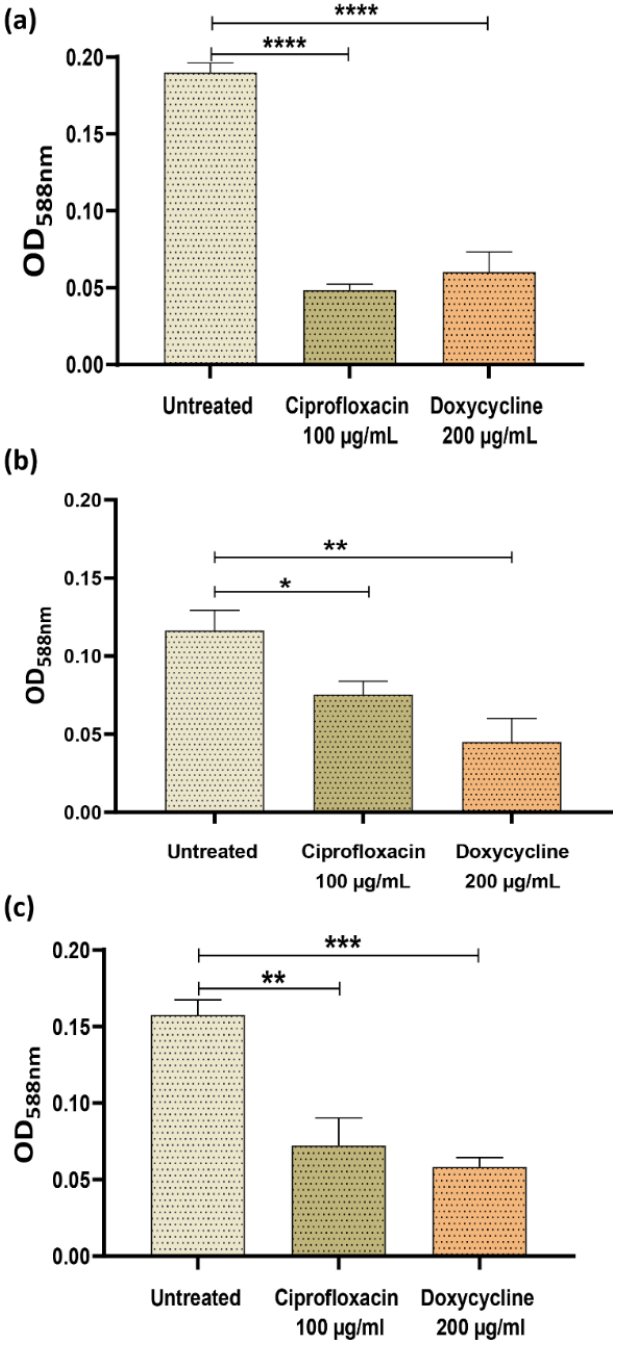


**Figure 3.** Formation of *E. coli*, *E. faecalis*, and dual-species biofilms under Control (untreated) and antibiotic-coated catheters: (a) *E. coli* shows inhibition under ciprofloxacin coating (100 µg/mL) and Doxycycline treatment (200 µg/mL) with a P value of 0.0001 and 0.0001 respectively (b) *E. faecalis* shows inhibition under Doxycycline (200 µg/mL) and ciprofloxacin treatment (100 µg/mL) with a P value of 0.0034, 0.0101 respectively. (c) Dual species exhibit inhibition

under Doxycycline (200 µg/mL) and Ciprofloxacin treatment (100 µg/mL) with a P value of 0.0001, 0.0019 respectively.

The MIC concentrations, such as 100 and 200 µg/mL of ciprofloxacin and doxycycline, were coated on the catheter surfaces and allowed to incubate for 48 h for the formation of *E. coli*, *E. faecalis*, and dual-species biofilms. After incubation, the biofilms were estimated at $OD_{588nm}$. Firstly, the $OD_{588nm}$ values for the *E. coli*, *E. faecalis*, and dual-species biofilms on the untreated catheter were found to be 0.19 ±0.006, 0.12 ± 0.013, and 0.16 ± 0.010 AU (Arbitrary Units), respectively. Secondly, the $OD_{588nm}$ values for the *E. coli*, *E. faecalis*, and dual-species biofilms on the ciprofloxacin (100 µg/mL) catheter were found to be 0.05 ± 0.004, 0.08 ± 0.009, and 0.07 ± 0.018 AU, respectively. Thirdly, the $OD_{588nm}$ values for the *E. coli*, *E. faecalis*, and dual-species biofilms on the doxycycline (200 µg/mL) catheter were found to be 0.06 ± 0.013, 0.05 ± 0.015, and 0.06 ± 0.006 AU, respectively. The values are plotted in the graph (Figure.3).

Finally, from the above data,100µg/mL of ciprofloxacin coating on the catheters reduces the formation of *E. coli*, *E. faecalis*, and dual-species biofilms by 74 % 35 %, and 54 %, respectively. Similarly, 200 µg/mL of doxycycline coating on the catheters inhibited the *E. coli*, *E. faecalis*, and dual-species biofilms by 68 %, 61 %, and 63 %, respectively. Therefore, it is clear that 200 µg/mL of doxycycline coating on the catheters inhibited the biofilm formation in both single and dual-species biofilm models. Also, 100µg/mL of ciprofloxacin coating on the catheters shows a potential biofilm formation reduction in *E. coli* biofilm models.

### *3.3 Ciprofloxacin and doxycycline coating to the catheters significantly reduces bacterial colonization*

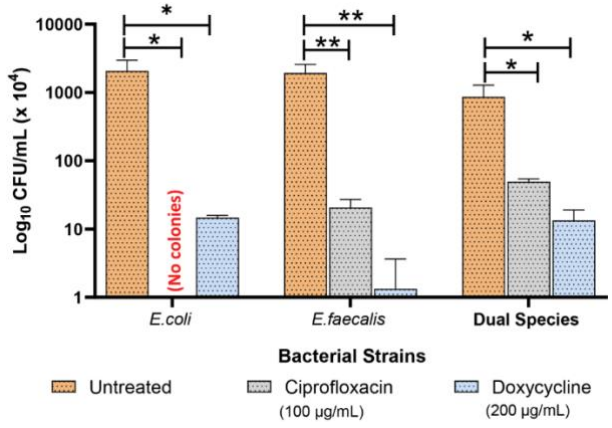


**Figure 4.** Estimation of Colony Forming Units on catheters coated with antibiotics (a) *E. coli* shows no growth under Ciprofloxacin (100 µg/mL) whereas under Doxycycline treatment (200 µg/mL) shows inhibition with a P value of 0.0166 (b) *E. faecalis* shows inhibition under Ciprofloxacin (100 µg/mL) and Doxycycline conditions (200 µg/mL) with P values of 0.067 and 0.0065, respectively. (c) Dual species exhibit inhibition under both Ciprofloxacin (100 µg/mL) and Doxycycline conditions (200 µg/mL) with a P value of 0.0273 and 0.0238, respectively.

After estimating the biofilm volume, the viable colonies were estimated using the CFU formula. Firstly, the CFU/mL values for the *E. coli*, *E. faecalis*, and dual-species biofilms on the untreated catheter were found to be 2066.7± 901.8, 1933.3±642.9, and 866.7±416.3CFU/mL, respectively. Secondly, the CFU/mL values for the *E. coli*, *E. faecalis*, and dual-species biofilms on the ciprofloxacin (100 µg/mL) catheter were found to be 0 (no colonies), 20.7± 6.4, and 49.3±5CFU/mL, respectively. Thirdly, the CFU/mL values for the *E. coli*, *E. faecalis*, and dual-species biofilms on the doxycycline (200 µg/mL) catheter were found to be 14.7± 1.2, 4, and 13.3±5.8CFU/mL, respectively. Finally, from the above data (figure.4), 100 µg/mL of ciprofloxacin coating on the catheters reduces the formation of *E. coli*, *E. faecalis*, and dual-species colonies by 100 %, 99 %, and 94 % at 10,000 dilutions, respectively. Similarly, 200 µg/mL of doxycycline coating on the catheters reduces the formation of *E. coli*, *E. faecalis*, and dual-species colonies by 99 %, 100 %, and 98 % at 10,000 dilutions, respectively. Therefore 200 µg/mL of doxycycline coating on the catheters inhibits the viable bacterial colonization in single and dual-species biofilm models (figure.4).

## 4. Conclusion

This study evaluates the required MIC for ciprofloxacin (100 µg/mL) and doxycycline (200 µg/mL) to inhibit single species (*E. coli* and *E. faecalis*) and dual species (Figure.2). The catheters coated with ciprofloxacin at 100 µg/mL reduces the formation of *E. coli*, *E. faecalis*, and dual species biofilms by 74 %, 35 %, and 54 %, respectively, while the doxycycline catheters coated at 200 µg/mL reduces the formation of *E. coli*, *E. faecalis*, and dual species biofilms by 68 %, 61 %, and 63 %, respectively (Figure.3). The viable colonies for the biofilms were found to be 2066.7± 901.8, 1933.3±642.9, and 866.7±416.3 on the untreated catheter for the *E. coli*, *E. faecalis*, and dual species, whereas for ciprofloxacin coated catheters at 100 µg/mL reduces the formation of *E. coli*, *E. faecalis*, and dual species colonies by 100 %, 99 %, and 94 %, respectively (Figure.4). Similarly, 200 µg/mL of doxycycline coated catheters reduces the formation of *E. coli*, *E. faecalis*, and dual species colonies by 99 %, 100 %, and 98 % , respectively. So, it is clear that doxycycline-coated catheters show more significant inhibition in both single and dual-species biofilm formation and bacterial colonization. Therefore, this study demonstrates the usage of *in-vitro* catheter biofilm models to test the antimicrobial nature of any novel compounds rapidly. Furthermore, this study could eliminate the need for animal studies during the initial phase of clinical trials. In essence, catheters coated with antibiotics not only inhibit biofilm but also eliminate the need for frequent catheter replacement, which could also contribute effective management of medical wastes.

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## Conflict of interest

The authors declare no conflict of interest.

## Authors Contribution

Conception and design of the study: SS, AS, BK, DKG, RK, and KK. Acquisition of data: SS, AS, and BK. Analysis and/or interpretation of data: SS, AS, BK, and DKG. Drafting the manuscript: SS, AS, BK, and DKG, and Revising the manuscript critically for important intellectual content: SS, AS, BK, DKG, RK, and KK.

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