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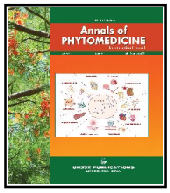

Original Article : Open Access

Unnoticed physiology of an angiotensin II receptor antagonist: Antioxidant, antimicrobial and antibiofilm activities of the drug Telmisartan against catheter-associated urinary tract infectious agents

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Abstract

One of the most encountered hospital-acquired infections, the catheter-associated urinary tract infection (CAUTI) is mostly linked to biofilm, making treatment critical resulting high rate of morbidity and mortality. As many of these infections are caused by multidrug-resistant microorganisms, there is an urgent for alternative antimicrobial agents. Therefore, telmisartan, an angiotensin II receptor blocker examined for its antimicrobial, and antibiofilm potentials against *Escherichia coli*, *Candida albicans*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* were predominantly reported organisms in CAUTIs. The telmisartan antimicrobial study revealed efficient activity against all the test pathogens using the agar diffusion method and the least inhibitory concentrations of telmisartan needed to stop the colony formation of *S. aureus* and *E. coli* were seen to be 31.2 µg/ml also, *P. aeruginosa* and *C. albicans* as it was 62.5 µg/ml. The antibiofilm activities of telmisartan were investigated by crystal violet staining method and exposed excellent antibiofilm activity by biofilm inhibition of all test pathogens. In addition, telmisartan efficiently eradicated 89%, 90%, 89%, and 92% against *P. aeruginosa*, *C. albicans*, *E. coli*, *S. aureus* and, respectively, after treated with 3X MIC concentration and also, telmisartan coating catheter tube had excellent antimicrobial activity against test organisms in *in vitro* bladder model. Further, telmisartan had excellent antioxidant properties. So, the author suggests that telmisartan may be used as an alternative agent for CAUTI treatment after detailed studies.

1. Introduction

Among the several healthcare-associated infections, catheter-associated urinary tract infections (CAUTI) are attaining much attraction owing to the continuous use of catheters in hospitalized patients for several days (Milo *et al*., 2019; Wooller *et al*., 2018; Saint *et al*., 2016; Guggenbichler *et al*., 2011). Catheters provide life support for hospitalized patients which is the main source of infections and also, increases the infectious risk in immune-compromised patients. Infections occurring in the sterile urinary tract are very common and lead to mild to severe complications that affect many people worldwide (Muhammad and Shamna, 2023; Papanikolopoulou *et al*., 2022; Flores-Mireles *et al*., 2019). The catheter was initially used for urine drain from the urinary system, but sometimes the urine block or uncompleted draining may create a suitable microenvironment for microbes' entry to the inner surface from the outer environment resulting in CAUTI (Yisiak *et al.,* 2021; Skelton-Dudley *et al*., 2019). The infections start from colonization on the catheter surface and form a biofilm structure which makes organisms stronger leading slightly to serious infection which extends the hospital stay and antibiotic overuse poses a serious socio-economic burden (Magill *et al*., 2018). Several causative agents are accountable for CAUTIs owing to their polymicrobial structures including bacteria like *E. coli, S. aureus,* and *P. aeruginosa* and fungi *C. albicans*) are mainly isolated organisms (Kurmoo *et al*., 2020; Di Martino, 2018). These prevalent organisms can form three-dimensional biofilm structures on the inner and outer catheter surface and these structures frequently reduce antibiotic susceptibility owing to the presence of extracellular polymeric substances embedded within the community which help the organism to escape from antibiotic treatment through antibiotic emission or reduced antibiotic uptake or altered target and also, change the host defense mechanism which may delay the treatment procedure (Muhammad *et al*., 2022; Peng *et al*., 2018; Tenke *et al*., 2017; Percival *et al*., 2015). Generally, CAUTI is curable by providing proper antibiotic treatment and catheter replacement is the excellent choice for CAUTI prevention, but numerous complications have been addressed due to recurring or inappropriate antibiotic use leading to resistant strain development resulting in treatment challenges (Maharjan *et al*., 2018). Therefore, this awful situation forced us to search for novel antimicrobials that have the potency to eliminate biofilm formation on inner and outer surfaces.

Nowadays, repurposing the already available drugs for other applications is one of the drug discovery approaches that gaining huge attention for innovative drug development (Thangamani *et al*., 2015). The main advantage of repurposing drugs over discovering or developing novel drugs is, that the repurposing drug has gone through many clinical trials to prove their efficacy, pharmacology, and safety profiles which decreases the cost, time, and risk (Chong and Sullivan,

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2007). Since several repurposing drugs have been reported for antimicrobial activity against many human pathogens, our study investigated telmisartan, which is an angiotensin II receptor blocker for its antimicrobial and antibiofilm activities against *S. aureus, P. aeruginosa, E. coli,* and *C. albicans* which are prevalent in CAUTIs.

2. Materials and Methods

2.1 Inoculum preparation

12-16 h old cultures of *S. aureus, E. coli, P. aeruginosa,* and *C. albicans* grown in Mueller Hinton Broth, Brain Heart Infusion Broth, and Sabouraud Dextrose Broth adjusted to 0.5 MacFarland unit were used. Here, positive controls such as rifampicin, ampicillin, and nystatin and vehicle control (sterile distilled water) were used, and the experiments were done in triplets.

2.2 Antimicrobial potentials of the drug telmisartan

The antimicrobial potential of the drug telmisartan against *S. aureus, E. coli, P. aeruginosa,* and *C. albicans* was determined by the well diffusion method (Meiyazhagan *et al*., 2016). Shortly, overnight cultures of the selected test microbes were swabbed over sterile respective Petri plates and allowed to receive two different concentrations of telmisartan in each well drilled on each plate and incubated. The antimicrobial efficiency of the drug telmisartan was calculated by measuring the growth inhibition zone around the well against *E. coli, S. aureus, P. aeruginosa,* and *C. albicans.*

2.3 Determination of MIC of the drug telmisartan

The telmisartan MIC against *E. coli, S. aureus, P. aeruginosa,* and *C. albicans* was calculated by the microdilution method (Meiyazhagan *et al*., 2015). In brief, the twofold serial dilution of 250 µg/ml of telmisartan was diluted in 96 well plates till the final concentration reached 1.95 µg/ml and incubated for turbidity observation after the culture's addition. Further, the turbidity of every well was used to measure the optical density at 600 nm.

2.4 Impact of the drug telmisartan on biofilm formation

The effect of the drug telmisartan on *E. coli, S. aureus, P. aeruginosa,* and *C. albicans* biofilm formation was studied by crystal violet assay (Meiyazhagan *et al*., 2015). In brief, test pathogens biofilm formations were monitored for five days in the well containing varying ranges of telmisartan concentrations between 250 µg/ml and 1.95 µg/ml, and the attached biofilm was allowed for methanol fixation and crystal violet staining for fixed biofilms. The final product obtained by destaining biofilms with an ethanol-acetone mixture was measured at 570 nm.

2.5 Influence of the drug telmisartan on biofilm eradication

The effect of telmisartan on *P. aeruginosa, S. aureus, E. coli,* and *C. albicans* mature biofilms was quantified through the crystal violet method (Meiyazhagan *et al*., 2015). Briefly, the mature biofilms of all the test pathogens were attained by allowing the overnight cultures to grow in respective broth for five days and that was allowed to react with 1X, 2X, and 3X MIC concentrations of telmisartan for 24 h. Then, methanol fixation for attached biofilms followed by crystal violet staining and the adding mixture of ethanol acetone to get the destained product. The obtained final product was measured at 570 nm.

2.6 Antimicrobial potentials of telmisartan-coated catheter

Telmisartan-coated catheter tube antimicrobial activity was studied using an *in vitro* bladder model against *P. aeruginosa, S. aureus, E. coli,* and *C. albicans* (Goda *et al*., 2022). The small piece of sterile catheter tube was coated with telmisartan placed over the test pathogen's lawned plates and incubated for zone formation around the tube which indicates the antimicrobial activity of the telmisartan-coated catheter against the above-mentioned test pathogens.

2.7 Antioxidant activities of the drug telmisartan

To find out the antioxidant properties of the drug telmisartan, by DPPH (2, 2-diphenyl-1-picryhydrazyl) free radical scavenging assay was used (Gayathri and Sathish, 2016). The varying concentrations were allowed to react with the DPPH solution for some time. The final reactant was measured at 517 nm and the percentage for radical scavenging potentials of the drug was calculated using the formula:

Scaenging activity = 100 × (control OD – test OD)/control OD

2.8 Statistical analysis

To predict the standard error, the mean and standard deviation were found for all the experiments.

3. Results

3.1 Antimicrobial potentials of the drug telmisartan

The different telmisartan concentrations of antimicrobial activities examined against *S. aureus, E. coli, P. aeruginosa,* and *C. albicans* through the well diffusion method are presented in Figure 1. A clear growth inhibition zone was noted around the well which was loaded with telmisartan in different concentrations. The results revealed the antimicrobial activity of telmisartan was dose-dependent evidenced by increasing size of zone formation against *P. aeruginosa, S. aureus, E. coli,* and *C. albicans.*

3.2 Determination of MIC of the drug telmisartan

The MIC of the drug telmisartan against *P. aeruginosa, S. aureus, E. coli,* and *C. albicans* calculated using the microdilution method is presented in Figure 2. The graph was plotted as the test concentrations against optical densities which indicate the minimum concentration that is required to stop the test pathogen's growth, and the calculated MICs of *P. aeruginosa* and *E. coli* were 62.5 µg/ml and 31.2 µg/ml, respectively. *S. aureus* and the fungus C. *albicans* also showed their MICs as 31.2 µg/ml and 62.5 µg/ml.

3.3 Effect of the drug telmisartan on biofilm formation

The effect of the drug telmisartan on the biofilm development by *P. aeruginosa, S. aureus, E. coli,* and *C. albicans* was quantified through crystal violet assay and the results are presented in Figure 3. A gradual increase of biofilm formation was documented against all the test pathogens, and maximum percentages of biofilm formation such as 92%, 78%, 75%, and 97% were noted against all test pathogens respectively which indicated antibiofilm activity of telmisartan.

3.4 Efficiency of the drug telmisartan on biofilm eradication

The effect of the drug telmisartan on *P. aeruginosa, S. aureus, E. coli,* and *C. albicans* mature biofilms studied on polystyrene surfaces is displayed in Figure 4. The figure indicates the biofilm eradicated percentage after treatment with three different concentrations 1X

MIC, 2X MIC, and 3X MIC of telmisartan against test pathogens. The results revealed that the drug telmisartan was able to maximize biofilm eradication at 90%, 89%, 89%, and 92% against *C. albicans* *S. aureus, E. coli,* and *P. aeruginosa* respectively after treatment with 3X MIC concentration which signifies the antibiofilm activity of the drug.

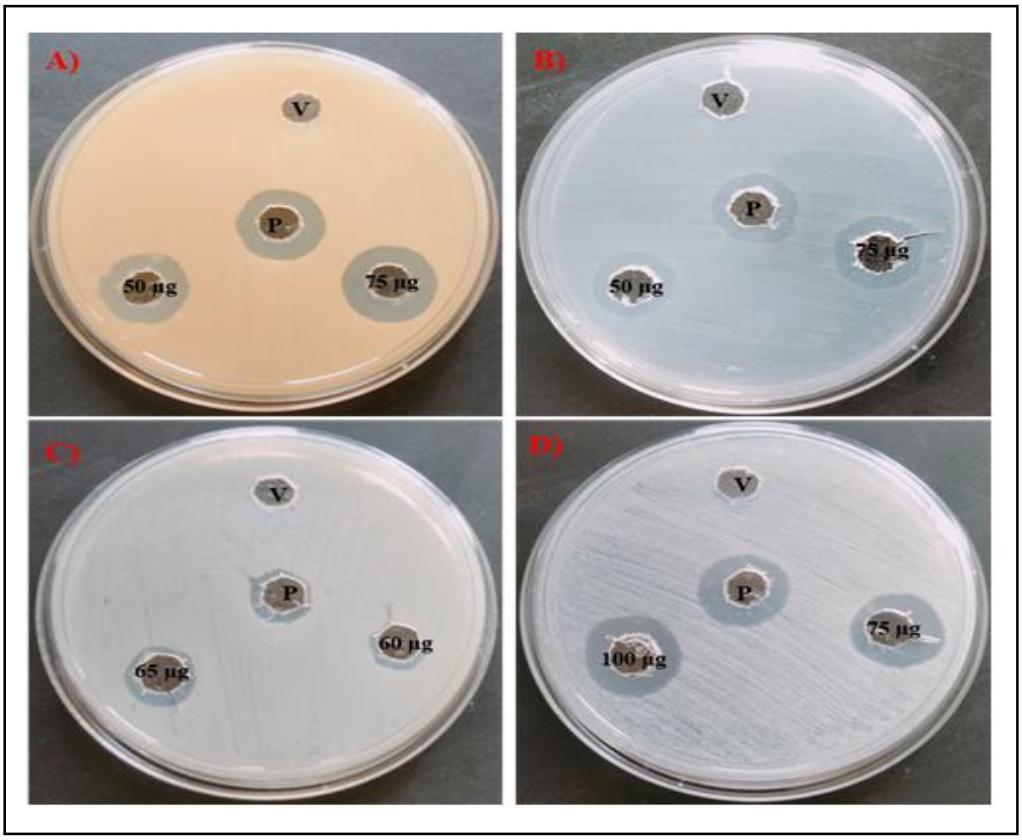

Figure 1: Antimicrobial activities of the drug telmisartan against (A) *S. aureus*, (B) *E. coli*, (C) *P. aeruginosa*, and (D) *C. albicans*.

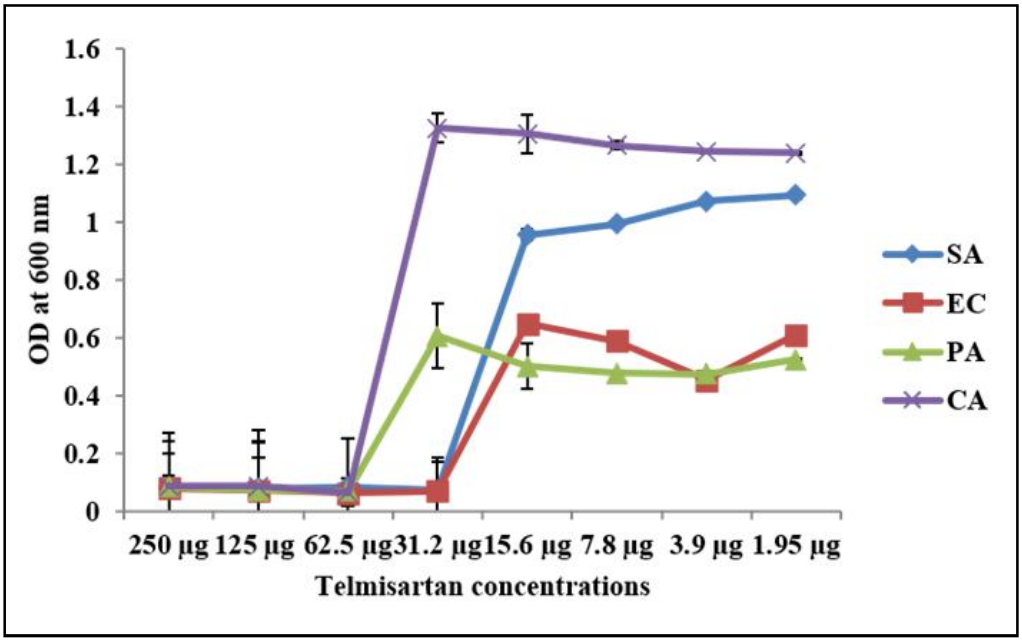

Figure 2: Telmisartan MIC determination against *S. aureus, E. coli, P. aeruginosa* and *C. albicans.*

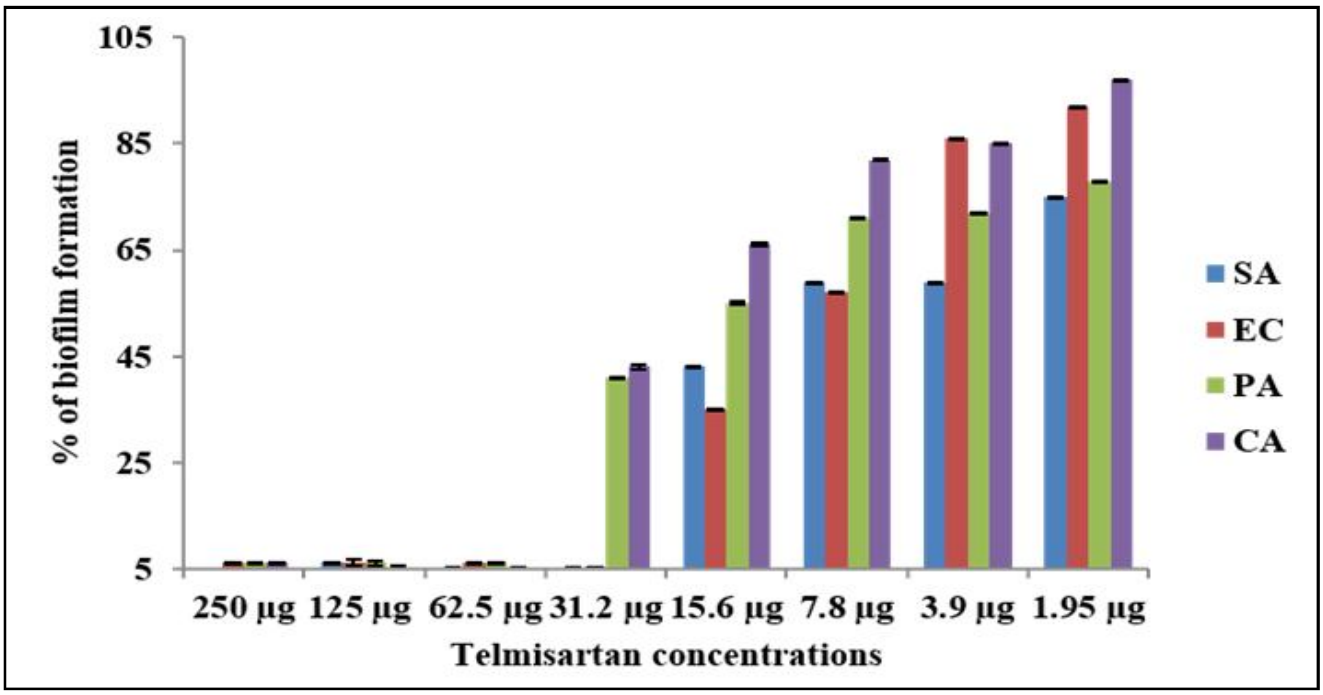

Figure 3: Quantification of telmisartan impression on *S. aureus, E. coli, P. aeruginosa* and *C. albicans* biofilm formation.

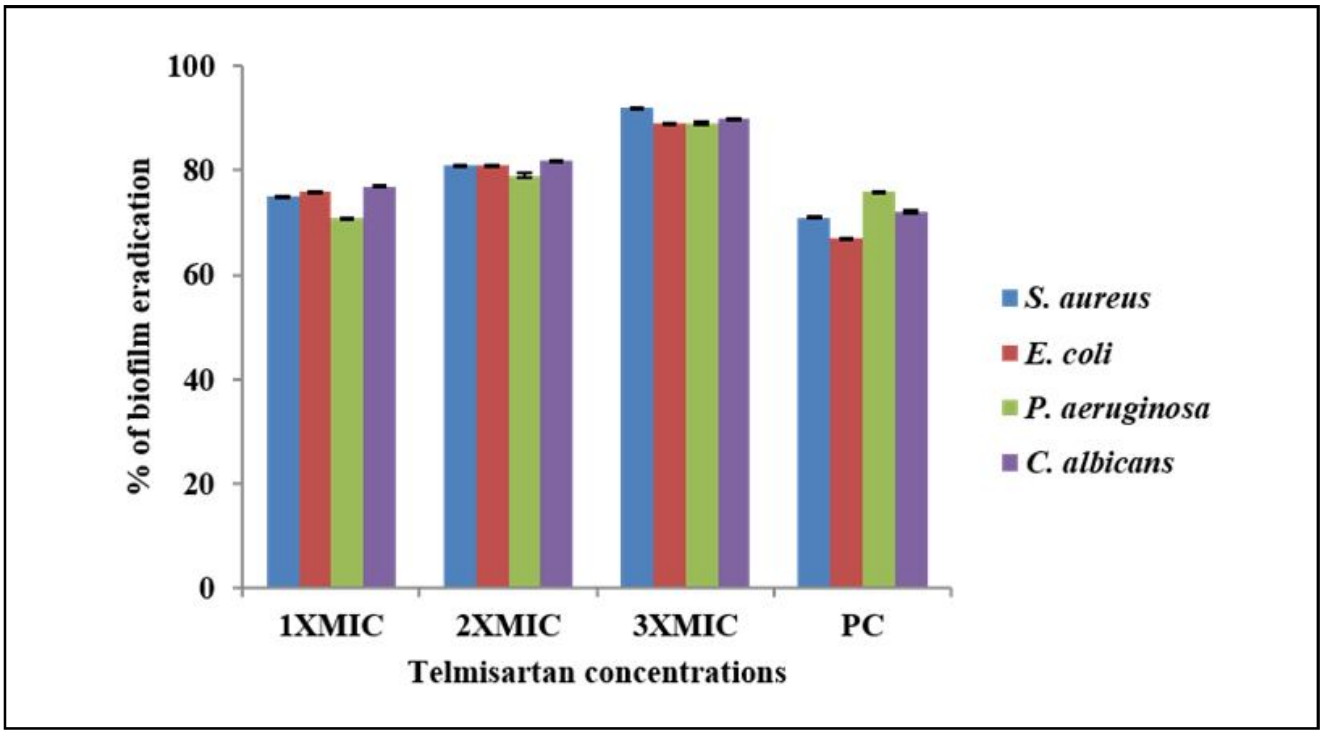

Figure 4: Percentage of *S. aureus, E. coli, P. aeruginosa*, and *C. albicans* biofilm eradication after telmisartan treatment.

3.5 Antimicrobial activities of telmisartan-coated catheter

The antimicrobial activity of telmisartan-coated catheter tubes assessed against *P. aeruginosa, S. aureus, E. coli,* and *C. albicans* through *in vitro* bladder is reported in Figure 5. The figure showed the clear zone around the telmisartan-coated catheter represents growth inhibition against test pathogens which proves the antimicrobial activity of telmisartan.

3.6 Antioxidant properties of the drug telmisartan

The antioxidant property of telmisartan was evaluated using DPPH and the calculated free radical scavenging activity percentage which

is displayed in Figure 6. Varying concentrations of the drug from 30 µg/ml to 150 µg/ml showed the free radical scavenging percentage as 7%, 27%, 29%, 38%, and 55% and the highest activity was detected at 150 µg/ml of telmisartan.

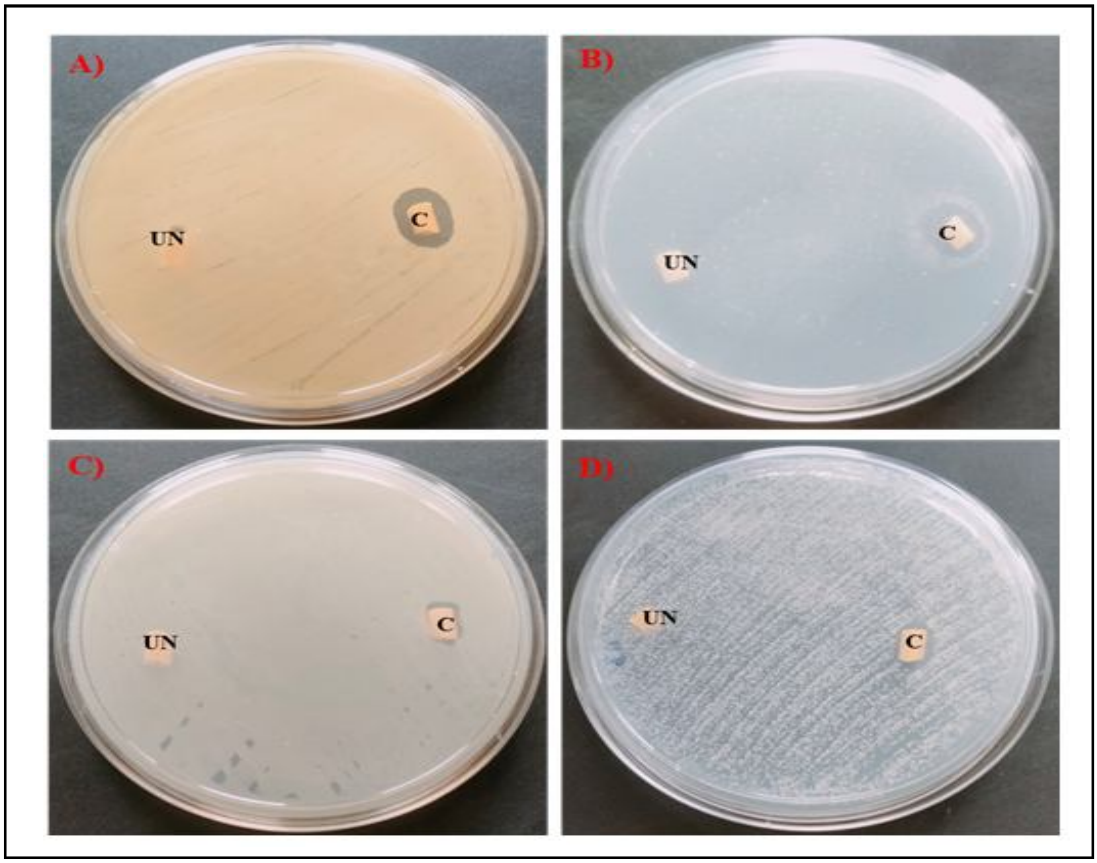

Figure 5: Telmisartan-coated catheter tube antimicrobial activity (A) *S. aureus*, (B) *E. coli*, (C) *P. aeruginosa*, and (D) *C. albicans*.

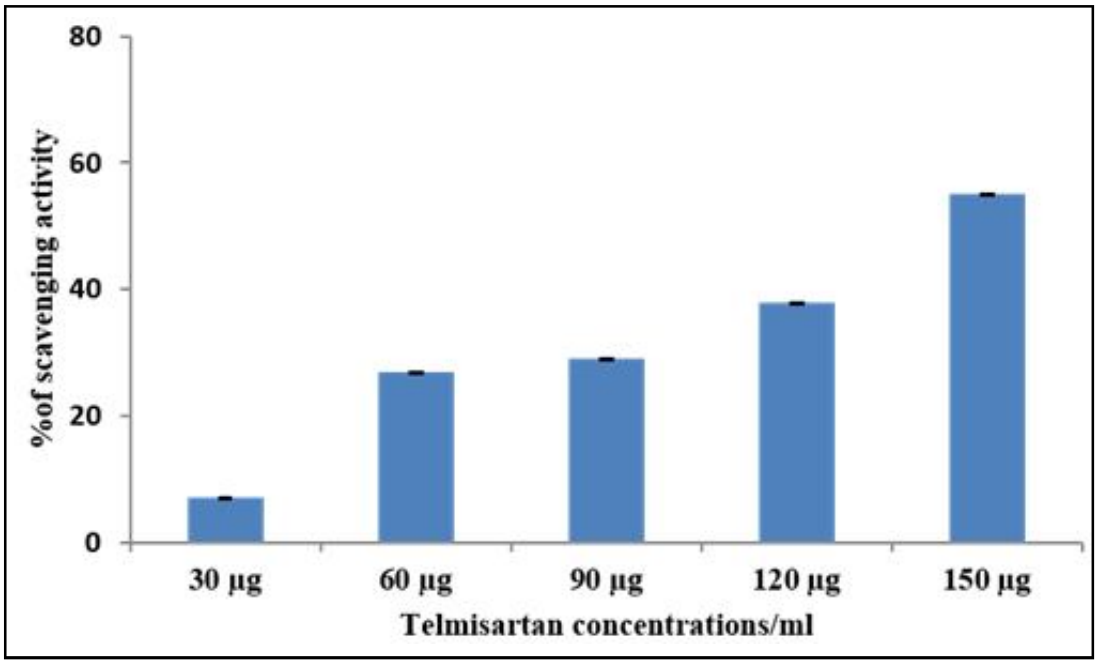

Figure 6: Percentage of free radical scavenging activity of telmisartan.

4. Discussion

CAUTI is mainly related to biofilm, which causes mild to serious complications in hospitalized patients and leads to severe complications resulting in treatment challenges, thereby increasing the mortality rate. Therefore, alternative antimicrobials with potent antibiofilm activity are urgently needed to prevent CAUTI. Hence, our study evaluated the antimicrobial activity of a repurposing drug, telmisartan against mainly prevalent organisms such as *E. coli, P. aeruginosa, S. aureus,* and *C. albicans*. Our study explored the antimicrobial potentials of the drug telmisartan against all the test pathogens and also showed the least concentration that is required for test pathogens' growth inhibition. Our findings were correlated with some recent studies wherein the antimicrobial activity of various repurposing drugs like fluoxetine, escitalopram, venlafaxine, mirtazapine, fluvoxamine and duloxetine were studied against many clinically relevant human pathogens like *E. coli, E. faecalis, S. aureus, Lactobacillus rhamnosus, Bifidobacterium* 791 and *Candida albicans* and also, showed potent inhibitory effect towards all the test pathogens. Moreover, the drugs fluvoxamine and escitalopram showed pronounced activity towards *E. coli, E. faecalis, and S. aureus* as well as minimum activity was found against *C. albicans* which indicates the drugs have excellent activities against bacterial pathogens compared to fungi whereas mirtazapine exhibited extreme activity against *C. albicans* when compared to bacteria suggesting this might be species-specific (Rukavishnikov *et al*., 2023). Similarly, an antidepressant drug, paroxetine exhibited potential antibacterial activities against methicillin-sensitive and resistant *S. aureus* with MIC of 64 µg/ml and the activity due to altered morphology of the pathogen when exposure to drugs (Cabral *et al*., 2023). In correlation, some repurposing drugs like auranofin, pentamidine, ebselen, temsirolimus, and fluoxetine have excellent antifungal activities against *Cryptococcus* sp. and *C. albicans* (Viveiro *et al*., 2024; Ajetunmobi *et al*., 2023; Lin *et al*., 2022; Pereira *et al*., 2021).

Further, CAUTI is mostly related to biofilm which encountered several stages including attachment, colonization, and maturation resulting in infections. Hence, the study examined the telmisartan effect on every stage of biofilm formation and found an excellent inhibitory effect by inhibiting biofilms on polystyrene surfaces. Also, it was again confirmed by eradicating mature biofilms of test pathogens suggesting the antibiofilm activity of telmisartan. The present study was supported by many research findings wherein duloxetine and diclofenac showed potent antibiofilm activity against *P. aeruginosa* and *S. aureus* by eradicating mature biofilm and inhibiting biofilms on non-living surfaces (Barbarossa *et al*., 2023; Periyasami *et al*., 2023). In addition, to suppress the biofilm formation on the catheter surface, coating the catheters with an antibacterial agent is an alternative and effective method. As a consequence of this, our study examined the coating ability of telmisartan against test pathogens and found excellent activity in the *in vitro* bladder model which imitates the suitable environment. Our findings were supported by other works wherein various antibacterial agents like duloxetine, zinc oxide, fosfomycin, polymer, silver and some antibiotic combinations were studied for coating ability against *E. coli, E. faecalis, P. aeruginosa* and *S. aureus* (Aleksandra *et al*., 2021; Jia *et al*., 2021; Rahuman *et al*., 2021; Abbott *et al.,* 2020; Fisher *et al*., 2015).

5. Conclusion

The telmisartan was evaluated for its antimicrobial activity against *S. aureus, E. coli, P. aeruginosa,* and *C. albicans* and found obvious antimicrobial activity with distinct inhibitory concentration against test pathogens. Further, telmisartan antibiofilm activity was demonstrated by biofilm formation inhibition and eradication of test pathogens. The telmisartan coating catheter antimicrobial activity exposed effective activity against test pathogens in a suitable condition. Altogether, telmisartan can be an alternative agent for treating CAUTI.

Acknowledgments

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Conflict of interest

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

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