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In Vitro Antibacterial, Anti-Biofilm Activities and Synergistic Effect of Amlodipine Against Healthcare-associated Infections (Hais)

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Abstract

The emergences of multi-drug resistant bacterial pathogens are rising worldwide which creates serious threat to human health. The scientists across the globe have recognised the seriousness of this issue and the world health organisation has warned about the consequences that will be faced. So, the search for alternate antibacterial agents with novel modes of action has been going on all over the globe. Repurposing an old drug for other application gained much attention as the drug would already be known for its physiological activities. Hence, in the study amlodipine, a hypertension drug investigated for its antibacterial activity against Staphylococcus aureus, Enterococcus faecalis and Escherichia coli. The amlodipine showed potent antibacterial activity and the minimum inhibitory concentration was calculated as 150 µg/ml for E. faecalis and E. coli and for S. aureus. The amlodipine has the ability to inhibit the biofilm formation and also effectively inhibited the mature biofilms after treatment. The synergistic activity of amlodipine with two existing antibiotics revealed the synergistic effect. Overall, the amlodipine had antibacterial, antibiofilm and synergistic activity proved that it could be a promising antibacterial agent against health care associated infections.

Keywords: *Antibacterial, Antibiofilm, Healthcare-Associated Infections Synergism, Amlodipine.*

Introduction

In the modern era, life threatening infections caused by multi drug resistant microbes has been emerged enormously which are serious threat to public health resulting severe socio-economic burden in most of the developed and developing countries. These microbes were developed resistance to different classes of antibiotics through various resistant mechanisms. The drastic increase of antimicrobial resistance is responsible for more than lakh deaths globally representing none of the novel antimicrobial agents are discovered by 2050, there will be a chance for more than a million death per year due to drug resistant organisms causing rigorous bacterial infection which is the primary cause of death (Yssel et al., 2017; Farha et al., 2019; Magill et al., 2014). Many of the life-threatening infection are mainly associated with biofilms that are general phenomenon which promotes the endurance and perseverance of clinically relevant pathogens on medical devices and tissues resulting chronic infections (Percival et al., 2015; Koo et al., 2017). The biofilms are structured microbial colonization with extracellular polymeric substances (EPS) which acting as a physical barrier to prevent the bacterial and antimicrobial interactions (Steven, 2016, Flemming et al., 2016) resulting antibiotics inactivation (Salgar-Chaparro et al., 2020). Numerous studies reported that nearly 80% of

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biofilms associated bacterial infections are showed high morbidity and mortality rate (Uruén et al., 2020; Banerjee et al., 2020; Jamal et al., 2018). The ability of multi drug resistant organisms forming biofilms on any living and non-living things makes treatment inefficient (Borges et al., 2013; Li et al., 2019). As a consequence, most of the healthcare related infections are associated with insertion of medical devices facing more challenges for treatment processes. Among the several biofilm forming organisms, Staphylococcus aureus, Enterococcus faecalis and Escherichia coli are most often isolated microbes in health care setting (Caldara et al., 2021). In the health care settings, the increases of multi drug resistant organisms severely delay the clinician's treatment options and treatment schedules (Aslam et al., 2018; Nathan et al., 2014). The biofilm forming microbes remains a most important crisis during the treatment process due to the antimicrobial resistant property it becomes a major concern for the development of novel of antibiotics against deadly infections (Bin et al., 2017). Therefore, the novel antimicrobial agents are needed to defeat the multi drug resistant organisms. But, the development of novel antimicrobial agents takes several processes to market the products and time consuming. Consequently, to reduce the time and cost, based on the earlier studies, repurposing an old drug for novel application is an effective method to eradicate biofilm related bacterial infections. The repurposing drugs are gaining much interest due to their safety and toxicological profile and their preclinical efficacy of these drugs are already known. Nowadays, many non-steroidal anti-inflammatory drugs were reported for their antimicrobial property against many clinically important pathogens including both gram positive and gram-negative infection (Paes and da Silva, 2021; Kaul et al., 2019; Zimmermann et al., 2019; Chan et al., 2017). Hence, in the study, the amlodipine, a drug used for treating hypertension was investigated for antibacterial, antibiofilm activity against S. aureus, E. faecalis and E. coli and also to overcome drug resistance, we also looked for the synergistic activity of amlodipine with commercially available antibiotics against biofilm forming microbes involved in health care associated bacterial infections.

Materials and Methods

Reagents

The Medias used in these studies such as like Mueller Hinton Agar (MHA) (Hi Media), Brain Heart Infusion agar (BHA) (Hi Media), ampicillin (Hi Media), rifampicin (Hi Media) was purchased and also the cultures like S. aureus (ATCC 25923), E. faecalis (ATCC 29212) and E. coli (ATCC 25922) were procured from American type Culture Collection Centre. For the study, the S. aureus and E. faecalis were grown in BHA and E. coli was grown using MHA. Ampicillin and rifampicin were used as positive controls. For each assay, overnight cultures of above-mentioned organisms were adjusted to 1x 10^6 CFU/ ml and also amlodipine (1 mg/ml) was used.

Antibacterial Activity Determination

The amlodipine antibacterial activity against S. aureus, E. faecalis and E. coli was evaluated by well diffusion method as described earlier (Meiyazhagan et al., 2015). In brief, the sterile MHA plate and BHI agar plates were swabbed with overnight cultures of test organisms and the created well on plate's surface was loaded with various amlodipine concentration and incubated for overnight. The zone of inhibition around the well indicated the antibacterial activity of amlodipine against test organisms.

MIC Determination

The amlodipine MIC was calculated using microdilution method against S. aureus, E. faecalis and E. coli as mentioned previously (Meiyazhagan et al., 2016). For the experiment, 150 µg/ml of amlodipine was serially diluted up to 1.15 µg/ml to and overnight cultures were added and incubated. The plate was observed for turbidity and the optical density at 600 nm using Spectrophotometer.

Amlodipine Effect on Formation of Biofilm

Amlodipine was observed for their effect on S. aureus, E. faecalis and E. coli biofilm formation in 96 well plates as described earlier (Meiyazhagan et al., 2015). For the study, amlodipine was serially diluted in respective broth and overnight cultures were added and allowed 5 days biofilm formation in the presence of amlodipine. After the period of biofilm formation, the biofilms were fixed with methanol after PBS wash and stained with crystal violet solution for 45 mins. The stained biofilms were washed and destained with ethanol acetone complex. Later, the final purple product was read spectrophotometrically at 570 nm and untreated wells served as negative control.

Amlodipine Effect on Mature Biofilms

The effect of amlodipine on S. aureus, E. faecalis and E. coli mature biofilms were investigated using crystal violet as mentioned earlier (Gowri et al., 2020). In brief, in 96 well plate each biofilm forming organisms were grown for 5 days and treated with two different concentrations (1X MIC and 2X MIC) of amlodipine. Later, the treated and untreated biofilms were washed and fixed with methanol followed by crystal violet staining for 45 mins. The ethanol and acetone complex were used to destain the biofilm and the obtained purple colored product was read spectrophotometrically at 570 nm and untreated wells served as negative control.

Synergistic Activity

The amlodipine synergistic activity was studied with commonly available antibiotics such as ampicillin for S. aureus and E. faecalis and rifampicin for E. coli using checker board assay as prescribed before (Meiyazhagan et al., 2016). The amlodipine and ampicillin and rifampicin were added as three concentrations below their MIC, equal to MIC and ONE above their MIC and the plate was incubated after the addition of test organism. Then, the incubated plates were spectrophotometrically measured and the synergistic effect was calculated using fractional inhibitory concentration index (FICI) by adding FIC of anastrozole and ampicillin and rifampicin.

Results

Amlodipine Antibacterial Activity

The antibacterial activity of amlodipine was analysed against S. aureus, E. faecalis and E. coli and the obtained results are presented in figure 1. As seen in figure, the zone of inhibition observed was measured in the entire well loaded with amlodipine indicating the antibacterial activity. The zone size increased gradually when increasing the amlodipine concentration against tested microbes.

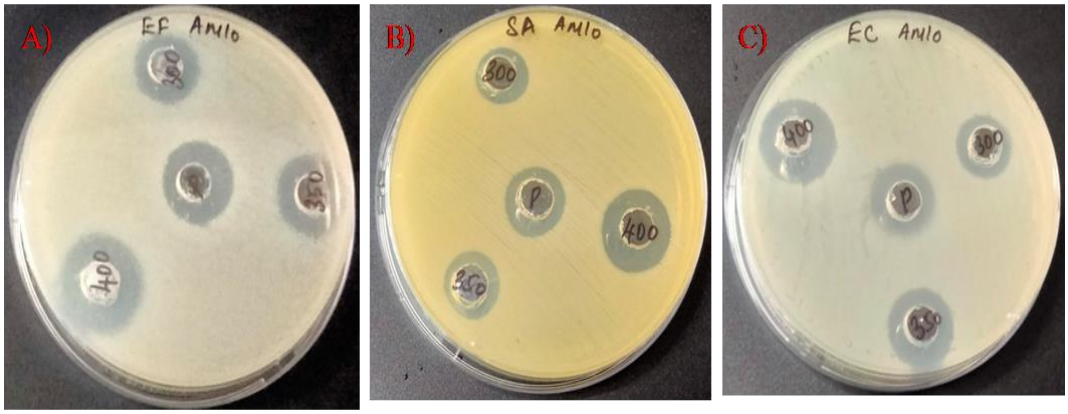

Figure 1: Amlodipine Antibacterial Activity a) E. Faecalis B) S. Aureus and C) E. Coli.

MIC Determination

The lowest concentration of amlodipine was evaluated against S. aureus, E. faecalis and E. coli and the calculated least inhibitory concentrations are plotted as graph in figure 2. The result revealed the lowest concentration for S. aureus growth inhibition was found to be 75 µg/ml of amlodipine whereas 150 µg/ml of amlodipine was needed for E. faecalis and E. coli growth inhibition.

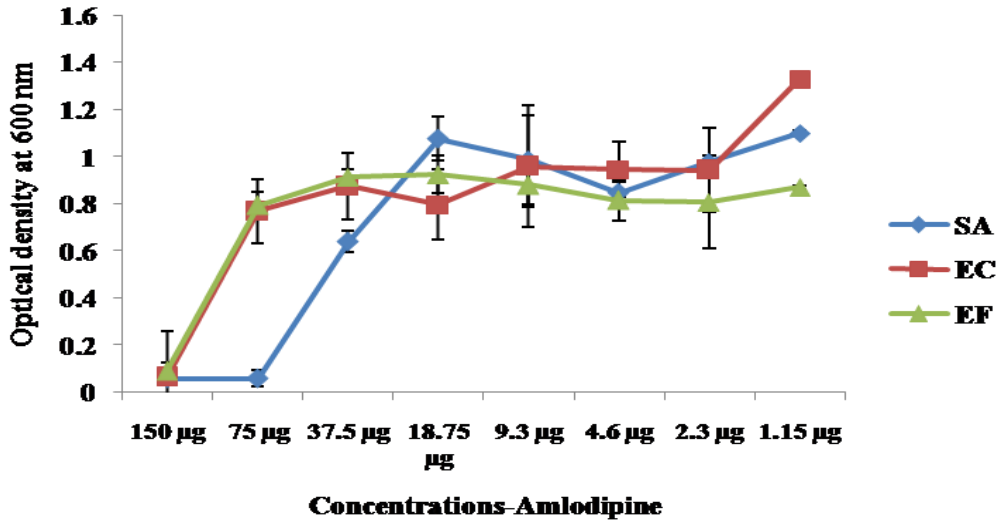

Figure 2: Determination of Mic Against S. Aureus, E. Faecalis and E. Coli.

Amlodipine Effect on Biofilm Formation

The amlodipine effect on biofilms formation of S. aureus, E. faecalis and E. coli was studied and the results are displayed in figure 3. As observed in figure, amlodipine has effectively inhibited the biofilm formation of tested microbes on non living surfaces up to their MIC concentrations. Whereas, the slow increase of biofilm formation was observed after their MIC level against S. aureus, E. faecalis and E. coli indicating that the traces of antibacterial agent can prevent the biofilm formation of tested organisms on various surfaces. The observed results suggested that the amlodipine has the ability to inhibit the biofilm formation.

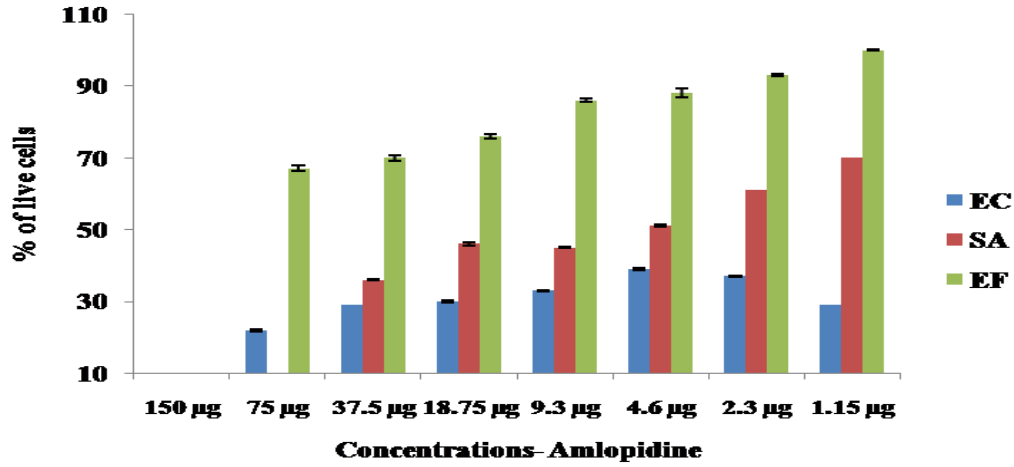

Figure 3: Amlodipine Effect on Biofilm Formation of S. Aureus, E. Faecalis and E. Coli.

Amlodipine Effect on Mature Biofilms

The amlodipine effect on mature biofilm after their treatment was studied using crystal violet method and the obtained results are presented in figure 4. The figure indicates the percentage of biofilm reduction after treatment with various concentrations of amlodipine against S. aureus, E. faecalis and E. coli on non living surfaces. Here, the amlodipine effectively eliminated 62% and 72% of E. faecalis mature biofilms after 1XMIC (150 µg/ml) and 2XMIC (300µg/ml) amlodipine treatment. Similarly, E. coli mature biofilms was eradicated as 73% and 77% after 1XMIC (150 µg/ml) and 2XMIC (300µg/ml) treatment. Whereas, amlodipine 1XMIC (75µg/ml) and 2XMIC (150µg/ml) concentrations reduced 59% and 66% of S. aureus mature biofilm on non living surfaces.

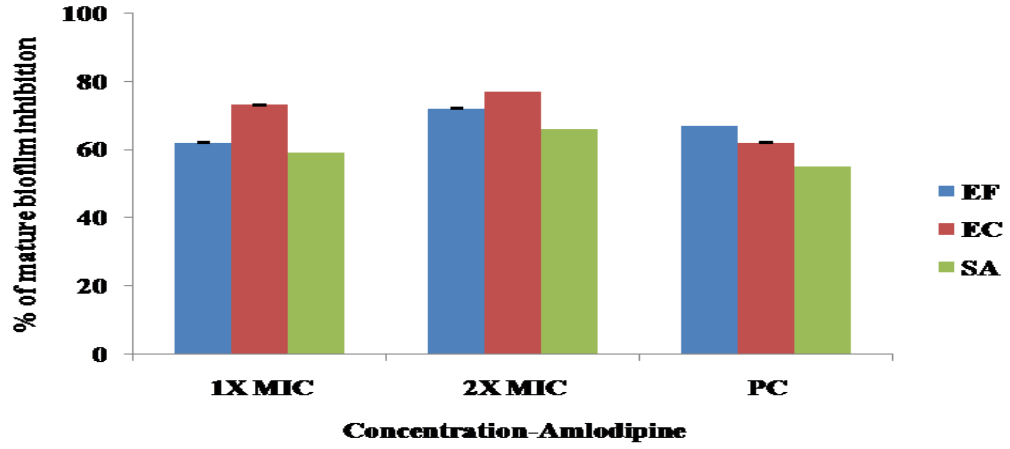

Figure 4: Anti Biofilm Activity of Amlodipine Against Mature Biofilms of S. Aureus, E. Faecalis and E. Coli.

Synergistic Activity

Amlodipine synergistic activity with two antibiotics such as ampicillin and rifampicin was

investigated against S. aureus, E. faecalis and E. coli and the results are presented in figure 5. As observed in figure, the MIC level was reduced from 150 µg/ml to 75 µg/ml against E. coli when amlodipine was combined with rifampicin. Same way, MIC level was reduced from 150µg/ml to 75 µg/ml against E. faecalis when amlodipine was combined with ampicillin. Similarly, the combination of amlodipine and ampicillin reduced the S. aureus MIC level from 75µg/ml to 18.75µg/ml. The FICI was calculated for amlodipine and showed synergistic effect which represents the amlodipine combination with other antibiotics for better treatment option.

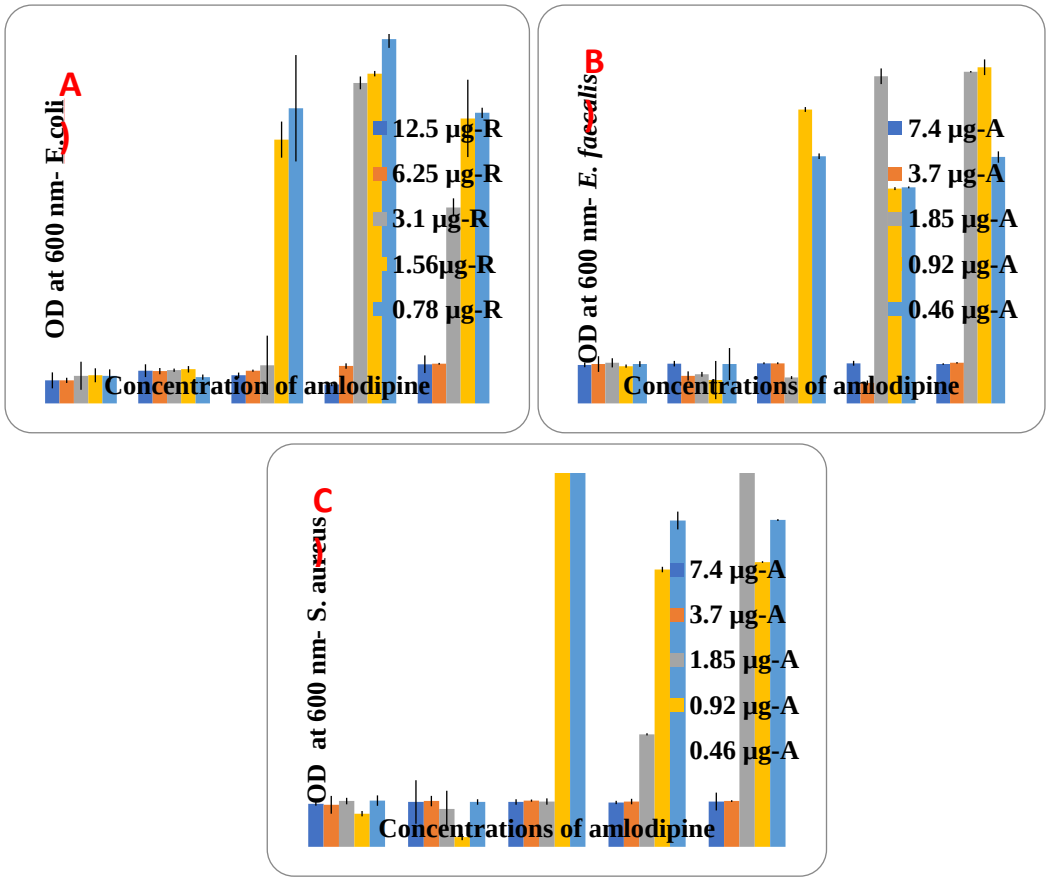

Figure 5: Synergistic Activity of Amlodipine with Ampicillin and Rifampicin.

Discussion

Novel methods are urgently needed to deal with the important public health threat of antimicrobial resistance which are rising up and the end up for existing antibiotics. Hence, our study evaluated the amlodipine, a hypertension drug for their novel application as antibacterial agent against S. aureus, E. faecalis and E. coli which are involved in health care settings. Our result revealed the potent antibacterial activity of amlodipine against S. aureus, E. faecalis and E. coli with MIC at 75 µg/ml and 150 µg/ml of for S. aureus E. faecalis and E. coli growth inhibition. Similarly, our results were correlated with earlier report wherein four non antibiotic drugs such as azelastine, amlodipine, sertraline and ebselen were evaluated against S. aureus

and found the better inhibitory activity at 200 µg/ml of azelastine, 64 µg/ml of amlodipine, 0.25 µg/ml of ebselen and 20 µg/ml of sertraline and good bactericidal activity against S. aureus indicating non antibiotic repurposing has a promising antibacterial activity against S. aureus (Boyd et al., 2021). Same way, antibacterial activity of Griseofulvin was evaluated against Gram-positive and Gram-negative micro-organisms and found the potent antibacterial activity MIC at 0.0037 to 0.04 mg/mL and good bactericidal activity at from 0.01 to 0.16 mg/mL suggested that this compound may used for better antibacterial agent against Gram-positive and Gram-negative micro-organisms (Geronikaki et al., 2020). These studies proved the repurposing drug antibacterial activity against various clinically important microbes.

Besides the antibacterial activity, amlodipine was looked for their anti-biofilm potency to inhibit the biofilm formation as well as their elimination on any living and non-living things because biofilm formation is an important process for microorganism to escape from any antibiotics treatment and it was started from attachment to maturation which makes health threat to public. Here, the amlodipine showed better antibiofilm activity by inhibiting the biofilm formation as well as eradicating the biofilm mature biofilm from non living surfaces. Our results were correlated with recent report wherein paroxetine antibacterial activity was studied alone and in combination with oxacillin against multi drug resistant S. aureus. The antibacterial activity of paroxetine was achieved at 64 µg/ml through various mechanisms of action which was evidenced in fluorescence microscopy; molecular docking and flow cytometry along the morphological changes were observed by scanning electron microscopy suggesting paroxetine was potential antibacterial agent against MDR S. aureus (Cabral et al., 2023). Similarly, antibacterial activity of hexestrol, a nonsteroidal synthetic estrogen was investigated against methicillin resistant S. aureus and showed effective inhibitory action in planktonic and biofilm-related MRSA infections. The antibacterial activity was achieved at 16 µg/mL and inhibited the adhesion property of MRSA through reducing the extracellular polymeric substances and the relative transcription levels of clfA, eno, pls, sacC and fnbpB. Also, hexestrol showed synergistic activity with aminoglycosides which represents the increase in the susceptibility pattern against S. aureus thereby hexestrol may be a promising antibacterial agent for MRSA infection (Liu et al., 2023).

Implementing a single drug for the treatment in the clinical setting seems to be less effective with rise of multi drug resistant species particularly biofilm forming S. aureus, E. faecalis and E. coli. Combination of one or more drugs for treating bacterial infection becoming an alternative method to reduce the morbidity associated infection and also reduction in emergence of resistant strains. Our study displayed synergistic activity with two antibiotics with reduced MIC values. More importantly, recent study evaluated in vitro antibacterial activity of carvedilol, amlodipine, amitriptyline against Acinetobacter baumannii infections caused by susceptible and multidrug-resistant strains and found the MIC values below 128 µg/ml of all the drugs. The synergetic effect revealed the Carvedilol-gentamicin (FICI 0.2813) and carvedilol-amlodipine (FICI 0.5625) were showed synergism suggested the use of drugs in lower level for the treatment of MDR strains (Ugurel and Turgut-Balik, 2023). Another study explored the antibacterial activity of two non-antibiotic drugs such as auranofin (rheumatoid arthritis drug) and pentamidine (antiprotozoal drug) alone and in combinations against multi drug resistant A. baumannii E. coli, and Klebsiella pneumonia. The study explored the strong synergistic antibacterial effect of two non-antibiotic drugs with FICI range between 0.094-0.506 by 1024-fold MIC reduction when auranofin combined with pentamidine and also, they revealed the bacterial membrane disruption resulting increased intracellular leakage after

treatment with drugs led effective killing of bacterial cells. Overall, the non-antibiotic drugs combination with antibacterial mechanisms gives a promising novel strategy to discover novel antibacterial drugs which delay drug resistance development. Overall, various studies proved the antibacterial, antibiofilm potential of repurposing drugs with better synergistic effect.

Conclusion

The amlodipine, a hypertension drug evaluated for their antibacterial, antibiofilm activities against S. aureus, E. faecalis and E. coli and also the synergistic effect of amlodipine was investigated with two antibiotics. The study revealed the potent antibacterial activity and it has the ability to inhibit biofilm formation. In addition, amlodipine was able reduce the mature biofilms of S. aureus, E. faecalis and E. coli on non living surfaces and the drug explored synergism with two existing antibiotics. On the whole, the amlodipine can be alternative treatment option for S. aureus, E. faecalis and E. coli infection in health care settings.

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Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of Data and Materials

The data are available upon request from the authors.

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