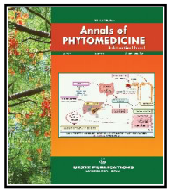
Annals of Phytomedicine 13(1): 843-849, 2024

DOI: http://dx.doi.org/10.54085/ap.2024.13.1.89

Annals of Phytomedicine: An International Journal
http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Original Article : Open Access

Antidepressant drug against bacterial pathogens: Effect of citalopram on biofilm forming hospital-acquired infectious (HAIs) agents

Khalid Albasheer*, Omer Munder*, Albagir Mahdi Ahmed Hassan, Hussein Khalifa*** and Mohammed H. Karrar Alsharif******◆

** Department of Obstetrics and Gynaecology, College of Medicine, Prince Sattam bin Abdulaziz University, Al-Kharj-11942, Saudi Arabia*
*** Department of Obstetrics and Gynaecology, Faculty of Medicine in Al-Qunphudah, Umm Al-Qura University, Saudi Arabia*
**** Department of Obstetrics and Gynaecology, Faculty of Medicine, Gadarif University, Gadarif, Sudan*
***** Department of Basic Medical Sciences, College of Medicine, Prince Sattam bin Abdulaziz University, Al-Kharj-11942, Saudi Arabia*

Article Info

Article history
Received 6 April 2024
Revised 23 May 2024
Accepted 24 May 2024
Published Online 30 June 2024

Keywords
Antidepressant
Citalopram
Drug repurposing
Hospital-acquired infectious (HAIs)
Minimal inhibitory concentrations
Multidrug resistance

Abstract

The development of multidrug resistance in bacterial pathogens in many ways including by the formation of biofilms has been considered as one of the major challenges that human beings face. As the biofilms form complex structures that help the bacteria to evade the host defense mechanisms resulting in serious socio-economic implications due to longer morbidity and higher mortality, there is an urgent need for new antimicrobial compounds with promising mechanisms of action. Drug repurposing is a novel method to find out the antibacterial activities of well-defined drugs in use, and here, citalopram, an antidepressant that comes under the SSRI category was investigated for its potential against three of the major hospital-acquired infection-causing bacteria, *viz*., *Enterococcus faecalis*, *Escherichia coli* and *Staphylococcus aureus*. In the present study, analyses were performed for the antimicrobial activities by well-diffusion protocols, for the minimal inhibitory concentrations (MICs) by microdilution method, the effect of the drug on pre-formed and mature biofilms by crystal violet method, synergic effects of the drug and selected antibiotics on the bacterial pathogens by checkerboard assay, *etc*., using standard protocols. The drug citalopram displayed potential activities against all of the selected bacterial pathogens and its MICs were found to be 62.5 µg/ml against *E. faecalis*, 125 µg/ml each against *S. aureus* and *E. coli*. The drug also showed remarkable antibiofilm activities and, at MIC levels, the eradication was 96.3%, 82% and 89% of mature biofilms by *S. aureus*, *E. coli* and *E. faecalis*. When combined with ampicillin and rifampicin, the drug citalopram displayed enhanced synergic effects against the pathogens. The drug was found to possess promising antibacterial and antibiofilm activities against three of the major hospital-acquired infections causing microbial pathogenic organisms, *viz*., *E. faecalis*, *S. aureus*, and *E. coli*. As the drug exhibited enhanced activities when combined with commercially available antibiotics, further studies could be conducted for a repurposed use of citalopram as an antibiotic.

1. Introduction

Many of the microorganisms are able to cause life-threatening infections and, more frequently, gain resistance to already available therapeutic agents, leading to antimicrobial resistance, which is considered to be a global threat to the public. As they limit the treatment options for the clinicians and disrupt their schedules, the infections by microorganisms showing antimicrobial resistance are difficult to treat and are accountable for more than 700,000 deaths worldwide, indicating that if no novel antibacterials are discovered by 2050, due to drug resistance itself, there can be above a million deaths per annum (Salam *et al*., 2023; Farha *et al*., 2019; Aslam *et al*., 2018; Yssel *et al*., 2017; Magill *et al*., 2014; Nathan *et al*., 2014). Thus, the consequence of the spread of drug-resistant organisms is the biggest global threat, which significantly contributes to higher morbidity and mortality (Walsh *et al*., 2023; Serwecińska 2020; Cassini *et al*., 2019; Gajdács, 2019). Among a number of life-threatening microbes, *E. faecalis*, *S. aureus,* and *E.coli* are among the most frequently encountered bacteria in healthcare settings (Banawas *et al*., 2023; Szabó *et al*., 2022; Caldara *et al*., 2021). The drug resistance may occur due to gene transfer mechanism, biofilm formation, efflux pumps, target site alternation, and enzyme inactivation that mediate resistance in organisms indicating that the defence mechanism of multidrug-resistant organisms has been broken already (Mahdyeh and Hossein, 2023; Mirghani *et al*., 2022; Chi' *et al*., 2022; Steven *et al*., 2016; Li and Nikaido, 2009). Developing novel antimicrobial agents against multidrug resistant organisms is an extremely time-consuming and expensive process that may take up to several years to complete, and as a consequence of this, the idea of discovering novel antimicrobial agents has been dropped by more than 50% (Silva *et al*., 2018; Rai *et al*., 2013; Silver, 2011). Owing to a drastic increase of drug resistance to commercially used antibiotics, researchers are now widely focusing the antimicrobial potentials of the drugs whose initial therapeutic action is not antimicrobial activity, and this repurposing has widely attracted as the drugs have already been tested for their efficacy and safety, and have been approved and promoted (Poyil and Bari, 2023; Kunz Coyne *et al*., 2022; Paes Leme *et al*., 2021; Schein, 2020). This

Corresponding author: Dr. Mohammed H. Karrar Alsharif
Department of Basic Medical Science, College of Medicine, Prince Sattam Bin Abdulaziz University, Al Kharj, KSA
E-mail: m.alshrif@psau.edu.sa
Tel.: +966-552644088

method can cut down the costs and may speed up the approval process, and it has been a hopeful approach to finding probable antimicrobial agents for treating infections that could be life-threatening (Krishnamurthy *et al*., 2022; Hua *et al*., 2022). Therefore, in the present study, the antibacterial, antibiofilm, and synergic potentials of an antidepressant non-antibiotic drug, citalopram, were investigated against *E. coli, E. faecalis,* and *S. aureus*.

2. Materials and Methods

2.1 Chemicals and reagents

For the study, the bacteriological media brain heart infusion agar (BHA), mueller hinton agar (MHA) and the antibiotics, including ampicillin and rifampicin were procured from Himedia laboratories private limited, India. The bacterial cultures of *E. faecalis* (ATCC 29212), *S. aureus* (ATCC 25923), and *E. coli* (ATCC 25922) were purchased from the ATCC (American type culture centre), and they were grown in respective media. The above-mentioned overnight cultures, which were adjusted to 1X106 CFU/ml, were used throughout the study.

2.2 Antibacterial potentials of the drug citalopram

The antibacterial potentials of the antidepressant drug citalopram were determined against three bacterial pathogens, *viz., E. faecalis, S. aureus,* and *E. coli* using the well-diffusion method (Meiyazhagan *et al*., 2015). Shortly after, the overnight cultures were swabbed on the sterile surfaces of the BHI agar and the MH agar, and the wells were drilled. Each well was loaded with various concentrations (250 µg/ml, 125 µg/ml, 62.5 µg/ml, 31 µg/ml, 15.5 µg/ml, 7.75 µg/m, 3.8 µg/m, 1.9 µg/ml) of citalopram and incubated. The antibacterial efficiency of citalopram was calculated by measuring the zones of inhibition around the well against *E. faecalis, S. aureus* and *E. coli*. Ampicillin and rifampicin were the positive controls.

2.3 Determination of minimal inhibitory concentrations (MICs) of citalopram against the pathogens

The drug citalopram was analyzed for its MICs against each of the selected bacterial pathogens using the microdilution method (Meiyazhagan *et al*., 2016). In brief, in a 96-well plate, 250 µg/ml of citalopram was serially diluted to make the concentration to 1.9 µg/ml in the respective broth. Later, overnight cultures of *E. faecalis, S. aureus,* and *E. coli* were added to the well, followed by incubation in standard conditions. Then, at 600 nm, the optical densities of the plates were read using a spectrophotometer.

2.4 Effect of citalopram on pre-formed biofilms

The drug citalopram was analyzed for its effect on pre-formed biofilms by the bacteria using polystyrene plates (Meiyazhagan *et al*., 2015). For the assay, the drug was subjected to serial dilution to reach a concentration of 1.9 µg/ml from 250 µg/ml in the respective broth, and the overnight cultures of *S. aureus, E. faecalis* and *E. coli* were added and incubated for 96 h to allow biofilm formation, followed by a phosphate buffered saline (PBS) wash and methanol fixation. Then the wells were stained with a crystal violet solution, washed with PBS and destained with ethanol-acetone complex. The untreated wells were the negative controls. The purple colour developed was spectrophotometrically analyzed at 570 nm.

2.5 Effect of citalopram on mature biofilms

To find out the antibiofilm effect of the drug citalopram on *E. faecalis, S. aureus* and *E. coli* mature biofilms, the biofilm formation assay was performed using crystal violet (Gowri *et al*., 2020). For the experiment, overnight cultures of *E. faecalis, S. aureus* and *E. coli* were added and incubated for 96 h to allow biofilm formation. After incubation, the mature biofilm was treated with three different concentrations of citalopram and allowed for 24 h. Then, with PBS, both the biofilms were washed, followed by methanol fixation, and then stained with crystal violet with ethanol-acetone complex. The untreated wells were the negative controls. Finally, the developed purple-coloured compound was read using a spectrophotometer at 570 nm.

2.6 Checkerboard assay for synergic effect analysis

To study the synergistic effect of citalopram with antibiotics in common use like rifampicin (against *E. coli*) and ampicillin (against *E. faecalis* and *S. aureus*), checkerboard assay was performed (Meiyazhagan *et al*., 2016). In brief, citalopram and the two antibiotics (rifampicin and ampicillin) were taken at concentrations, one above the MIC, the other at MIC, and three below MIC in combinations followed by the addition of overnight cultures of *E. coli, S. aureus*, *E. faecalis,* and incubated. Later, the plate was read spectrophotometrically at 600 nm, and the synergistic effect was studied by calculating the FICI (fractional inhibitory concentration index) by adding FIC of ampicillin, citalopram and rifampicin. Here, the FIC of citalopram was obtained by dividing the MIC of citalopram in combinations with their original MIC.

2.7 Statistical analysis

For all the experiments, mean and standard deviations were performed to calculate the standard error.

3. Results

3.1 Antibacterial potential determination

The antibacterial potentials of the drug citalopram were determined against *E. faecalis*, *S. aureus,* and *E. coli,* and the zones of inhibition are shown in Figure 1. The citalopram exhibited antibacterial activity in all the tested concentrations against the above-mentioned organisms and was determined by observing the zone of inhibition around the well. The inhibition areas were bigger when the concentration of the drug citalopram against the bacteria was increased.

3.2 Determination of minimal inhibitory concentration (MIC)

The minimal inhibitory concentrations of the drug citalopram were calculated against *E. faecalis, S. aureus,* and *E. coli* using the microdilution method and are represented graphically (Figure 2). As seen in the graph, 62.5 µg/ml of citalopram was needed to inhibit the *E. faecalis* growth, and 125 µg/ml of citalopram was needed for the inhibition of *S. aureus* and *E. coli* growth.

3.3 Citalopram effect on preformed biofilm

The effect of the drug citalopram was studied on preformed biofilms of *E. faecalis, S. aureus,* and *E. coli,* and the inhibitory effects are presented in Figure 2. As indicated in the figure, the citalopram displayed potential efficiency in inhibiting bacterial biofilm formation at their MIC level, and the gradual increase of *S. aureus* biofilm formation was noted after their MIC level. Fortunately, a trace of

citalopram can slow down the *E. faecalis* and *E. coli* biofilm formation on non-living surfaces, indicating the potency of citalopram in preventing biofilm formation, with no growth of any organisms at the first two higher concentrations.

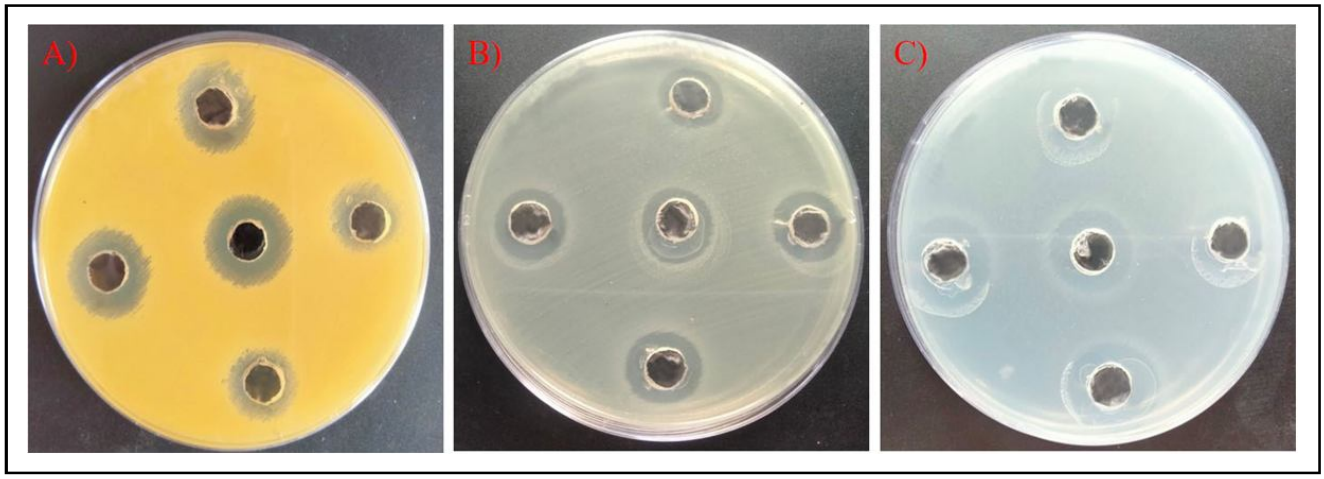


Figure 1: Citalopram antibacterial activity against: A. *S. aureus*, B. *E. faecalis* and C. *E. coli*.

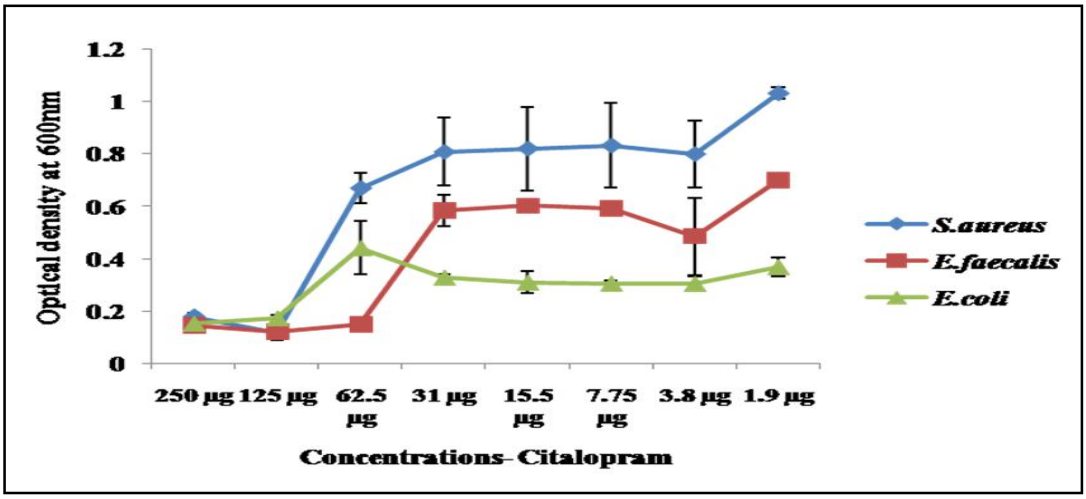


Figure 2: Citalopram least inhibitory concentrations against *S. aureus*, *E. faecalis* and *E. coli*.

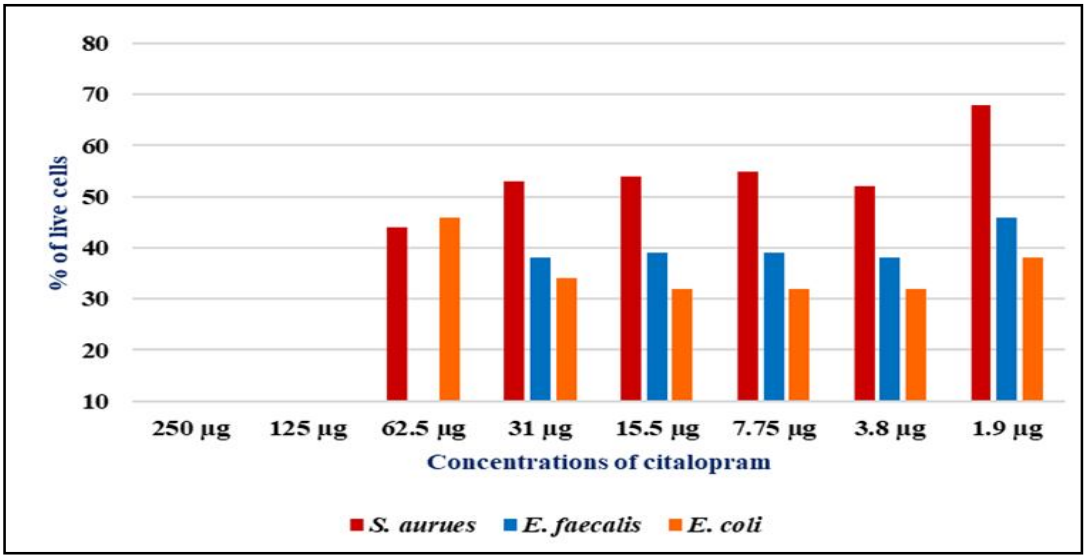


Figure 3: Citalopram impact on preformed biofilms of *S. aureus*, *E. faecalis* and *E. coli*.

3.4 Effect of citalopram on mature biofilms

The effect of the drug citalopram on mature biofilms of *E. faecalis, S. aureus,* and *E. coli was* studied and quantified using crystal violet, and the calculated percentage of biofilm reduction is shown in Figure 5. As clearly seen in the figure, various concentrations (1X MIC, 2X MIC, and 3X MIC) of citalopram reduced the mature biofilm effectively. The citalopram effectively reduced 86%, 89%, and 96.3% of *S. aureus* biofilm after treatment with 1X MIC (125 µg /ml), 2X MIC (250 µg/ml), and 3X MIC (375 µg/ml), respectively. Similarly, 84%, 89%, and 89% of *E. faecalis* biofilm reduction were observed after treatment with various concentrations 1X MIC (62.5 µg/ml), 2X MIC (125 µg/ml), and 3X MIC (187.5 µg/ml) of citalopram. Whereas, citalopram effectively inhibited 79%, 81%, and 82% of *E. coli* biofilm after treatment with 1X MIC (125 µg/ml), 2X MIC (250 µg/ml), and 3X MIC (375 µg/ml), indicating the citalopram potency in removing biofilms.

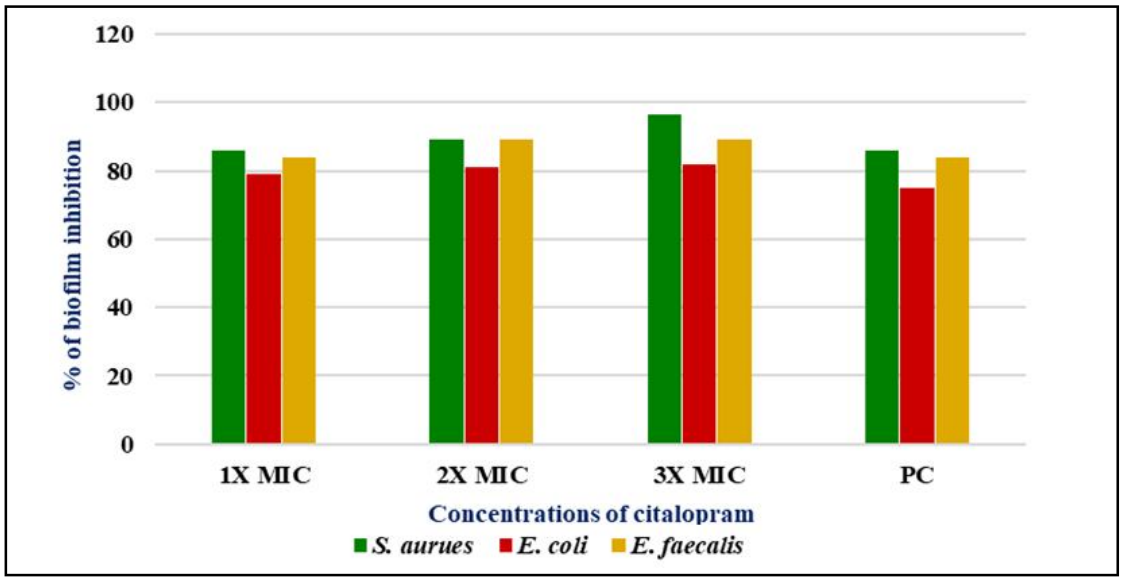
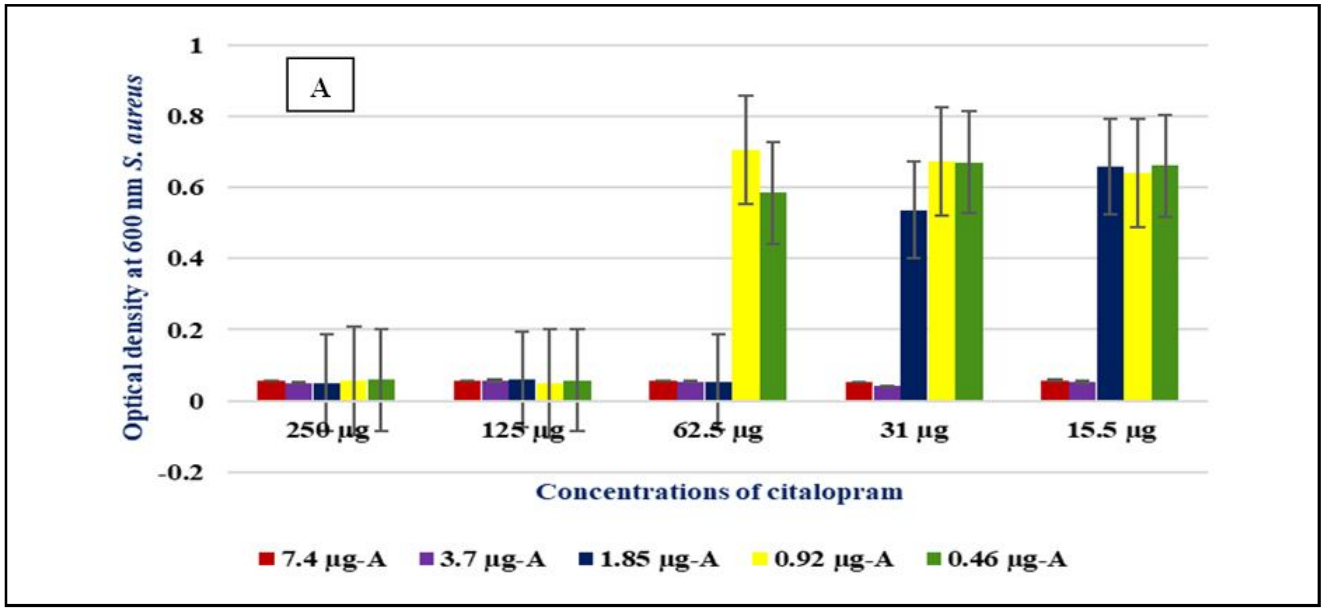


Figure 4: Citalopram impact on mature biofilms of *S. aureus, E. faecalis,* and *E. coli* (Note: PC-positive control).

3.5 Checkerboard assay

The synergistic effect of citalopram with already known antibiotics (ampicillin and rifampicin) was studied, and the findings are shown in Figure 5. The level of MIC declined when the citalopram was added along with ampicillin from their original MIC (125 µg /ml) to 62.5 µg/ml against *S. aureus*; while *E. faecalis* was treated with citalopram in combination with ampicillin, showing a decrease in their MIC level from 62.5 µg/ml to 31 µg/ml. In the same way, when *E. coli* was treated in combination with rifampicin, it could reduce the minimal inhibitory concentration required against the organisms to 62.5 µg/ml, from an initial level MIC of 125 µg/ml when only one drug was drug was used. The fractional inhibitory concentration index (FICI), which indicates a lack of substantial interaction between these antimicrobial agents was determined for both drugs as 0.5, indicating a synergistic effect.



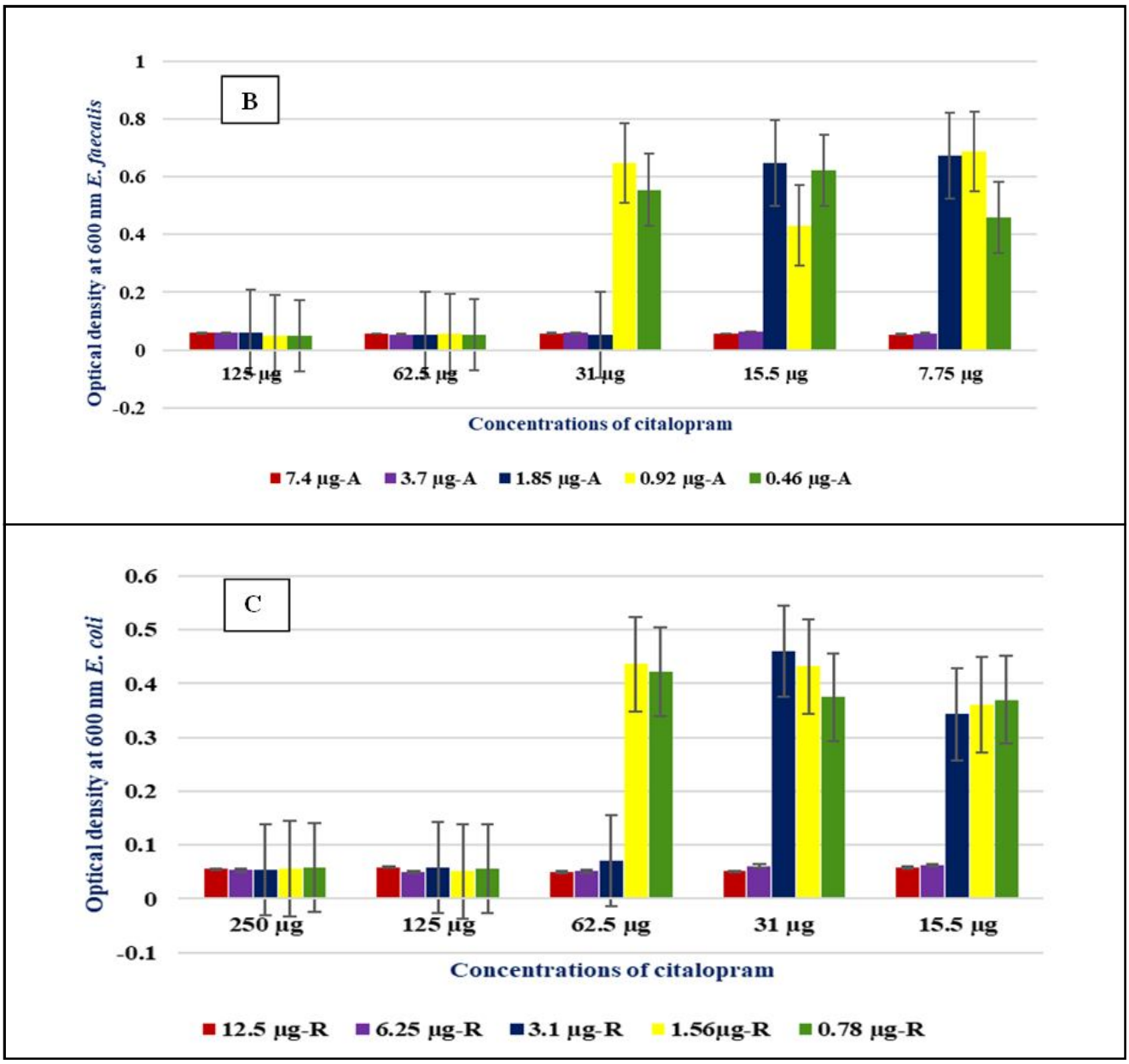


Figure 5: Combined effect of citalopram with ampicillin and rifampicin.

4. Discussion

The emerging multidrug-resistant organisms to many classes of antibiotics create a serious threat to human health, resulting in high morbidity and mortality. The occurrence of multidrug-resistant organisms is mainly related to biofilms, making treatment difficult (Ying *et al*., 2021). So, there is a need for alternative antimicrobials to overcome multidrug resistance and eradicate biofilms. Therefore, citalopram, an antidepressant drug, was evaluated for its antibacterial and antibiofilm activity against hospital-associated infections causing microbes such as *S. aureus, E. faecalis, and E. coli*. Many repurposing drugs have a successful clinical treatment ratio against fungi and bacteria (Muthu *et al*., 2020; Vidya *et al*., 2022). Our study also again proved the antibacterial and antibiofilm activity of citalopram against tested organisms, indicating the repurposing drugs applications beyond their original approved use. Also, citalopram showed a synergistic effect with rifampicin and ampicillin. Similarly, various antidepressant drugs such as escitalopram, fluoxetine, duloxetine, mirtazapine, fluvoxamine, and venlafaxine against common gut microbes, including *S. aureus, E. faecalis, Lactobacillus rhamnosus, E. coli, Bifidobacterium* and *Candida albicans* (Rukavishnikov *et al*., 2023). All the tested antidepressants showed activity against all the tested microbes. Among them, venlafaxine and fluvoxamine had the very least effect on *C. albicans E. faecalis, E. coli,* and *S. aureus.* Also, escitalopram had the greatest effect on *E. faecalis, E. coli, L. rhamnosus, B. bifidum,* and *C. albicans,* which confirmed the effect of antidepressant drugs against gut microbes, and it has novel directions as an antibacterial agent (Rukavishnikov *et al*., 2023). Recently, a non-steroidal synthetic estrogen drug,

hexestrol, was evaluated against methicillin-resistant *S. aureus* for its antibacterial and antibiofilm effect. It showed excellent antibacterial activity with MIC of 16 µg/ml, effectively reducing the biofilm and exhibiting synergism with antibiotics (Liu *et al*., 2023). In the same way, the drug selamectin was analysed for its antimicrobial potential against *S. aureus,* and a change in cell morphology was observed also after treatment. Then, it effectively reduced the biofilm formation and showed a synergistic effect with ampicillin (Folliero *et al*., 2023). Similarly, another repurposing drug, paroxetine, was evaluated for antimicrobial potentials against both methicillin-resistant and methicillin-sensitive *S. aureus,* and its synergistic effect was investigated. The drug showed antibacterial activity with MIC of 64 µg/ml and had additive interactions with oxacillin. The mechanism of action revealed the morphological changes (Cabral *et al*., 2023). *In vitro,* the antimicrobial efficiency of the drug amlodipine was investigated against *S. aureus* and found antibacterial activity at 128 µg/ml. The synergistic effect was analyzed with oxacillin and also showed antibiofilm activity against mature biofilm. The activity achieved through membrane damage leads to cell death (Barbosa *et al*., 2023). Another study proved the antibacterial activity of escitalopram oxalate and their interaction with the DNA of bacteria and showed hyperchromism. The drug showed antibacterial activity against *Bacillus subtilis* and *E. coli* with the least inhibitory concentrations of 0.185 mM and 0.55 mM, respectively (Valipour *et al*., 2019). A study investigated the two repurposing drugs such as escitalopram oxalate and clonazepam antibacterial activity alone and in combinations with known antibiotics ciprofloxacin and trimethoprim. They proved the antibacterial activity, minimum inhibitory concentrations, and fractional inhibitory concentrations were determined against Gram-positive organisms and also had synergistic effects with antibiotics (Rosa *et al.,* 2021).

5. Conclusion

An antidepressant drug, citalopram, was investigated for its antibacterial activity against common hospital pathogens like *S. aureus, E. faecalis,* and *E. coli.* Citalopram exhibited antimicrobial potential, and the minimum inhibitory concentrations were calculated. Citalopram effectively inhibited the biofilms and excellently eradicated the mature biofilms by *E. coli, S. aureus* and *E. faecalis*, after the treatment. The combination study proved the synergistic effect of citalopram with ampicillin and rifampicin. Overall, the study proved the antibacterial activity, antibiofilm activity, and synergistic effect of citalopram, suggesting that it can be a better alternative antibacterial agent when it is combined with any of these tested antibacterials for better treatment against bacterial infections.

Acknowledgements

The authors are grateful to the Deanship of Scientific Research, Prince Sattam bin Abdulaziz University, Al-Kharj, Saudi Arabia, for its support and encouragement in conducting the research and publishing this report.

Conflict of interest

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

References

Aslam, B.; Wang, W.; Arshad, M.I.; Khurshid, M.; Muzammil, S.; Rasool, M.H.; Nisar, M.A.; Alvi, R.F.; Aslam, M.A. and Qamar, M.U. (2018). Antibiotic resistance: A rundown of a global crisis. Infect. Drug Resist., **11**:1645-1658.

Banawas, S.S.; Alobaidi, A.S.; Dawoud, T.M.; AlDehaimi, A.; Alsubaie, F.M.; Abdel-Hadi, A. and Manikandan, P. (2023). Prevalence of multidrug-resistant bacteria in healthcare-associated bloodstream infections at hospitals in Riyadh, Saudi Arabia. Pathogens, **12**:1075.

Barbosa, A.D.; Sá, L.G.; Neto, J.B.; Rodrigues, D.S.; Cabral, V.P.; Moreira, L.E.; Aguiar, L.G.; Santos, H.S.; Cavalcanti, B.C.; Marinho, E.S.; Silva, J.; Magalhães, H.I.; Moraes, M.O.; Júnior, H.V. and Silva, C.R. (2023). Activity of amlodipine against *Staphylococcus aureus*: Association with oxacillin and mechanism of action. Future Microbiol., **18**:505-519.

Cabral, V.P.; Rodrigues, D.S.; Barbosa, A.; Moreira, L.E.; Sá, L.G.; Silva, C.R.; Neto, J.B.; Silva, J.; Marinho, E.S.; Santos, H.S.; Cavalcanti, B.C.; Moraes, M.O. and Júnior, H.V. (2023). Antibacterial activity of paroxetine against *Staphylococcus aureus* and possible mechanisms of action. Future Microbiol., **18**:415-426.

Caldara, M. and Marmiroli, N. (2021). Antimicrobial properties of antidepressants and antipsychotics-possibilities and implications. Pharmaceuticals, **14**:915.

Cassini, A.; Högberg, L.D.; Plachouras, D.; Quattrocchi, A.; Hoxha, A.; Simonsen, G.S.; Colomb-Cotinat, M.; Kretzschmar, M.E.; Devleesschauwer, B. and Cecchini, M. (2019). Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European economic area in 2015: A population-level modelling analysis. Lancet Infect. Dis., **19**:56-66.

Chi', A.A.; Rus, L.L.; Morgovan, C.; Arseniu, A.M.; Frum, A.; Vonica-incu, A.L.; Gligor, F.G.; Mure'an, M.L. and Dobrea, C.M. (2022). Microbial resistance to antibiotics and effective antibiotherapy. Biomedicines, **10**(5):1121.

Farha, M.A. and Brown, E.D. (2019). Drug repurposing for antimicrobial discovery. Nat. Microbiol., **4**:565-577.

Folliero, V.; Dell'Annunziata, F.; Santella, B.; Roscetto, E.; Zannella, C.; Capuano, N.; Perrella, A.; De Filippis, A.; Boccia, G.; Catania, M.; Galdiero, M. and Franci, G. (2023). repurposing selamectin as an antimicrobial drug against hospital-acquired *Staphylococcus aureus* Infections. Microorganisms, **11**(9):2242.

Gajdács, M. (2019). Extra deaths due to pan drug-resistant bacteria: A survey of the literature. Egészségfejlesztés, **60**:31-36.

Gowri, M.; Jayashree, B.; Jeyakanthan, J. and Girija, E.K. (2020). Sertraline as a promising antifungal agent: Inhibition of growth and biofilm of *Candida auris* with special focus on the mechanism of action *in vitro*. J. Appl Microbiol., **128**:426-437.

Gowri, M.; Sofi, B.W.; Biswal, J.; Dhamodharan, P.; Saiharish, R.; Rohan, P.S.; Pitani, R.; Kandaswamy, D.; Raghunathan, R.; Jeyakanthan, J.; Rayala, S.K. and Venkatraman, G. (2016). β-lactam substituted polycyclic fused pyrrolidine/pyrrolizidine derivatives eradicate *C. albicans* in an ex *vivo* human dentinal tubule model by inhibiting sterol 14-α demethylase and cAMP pathway. Biochim Biophys Acta., **1860**:636-647.

Krishnamurthy, N.; Grimshaw, A.A.; Axson, S.A.; Choe, S.H. and Miller, J.E. (2022). Drug repurposing: A systematic review on root causes, barriers and facilitators. BMC Health Serv. Res., **22**(1):970.

Kunz Coyne, A.J.; El Ghali, A.; Holger, D.; Rebold, N. and Rybak, M.J. (2022). Therapeutic strategies for emerging multidrug-resistant *Pseudomonas aeruginosa*. Infect. Dis. Ther., **12**:1-22.

Liu, S.; She, P.; Li, Z.; Li, Y.; Li, L.; Yang, Y.; Zhou, L. and Wu, Y. (2023). Antibacterial and antibiofilm efficacy of repurposing drug hexestrol against methicillin-resistant *Staphylococcus aureus*. Int. J. Med. Microbiol., **313**(2):151578.

Li, X.Z. and Nikaido, H. (2009). Efflux-mediated drug resistance in bacteria: An update. Drugs, **69**(12):1555-623.

Mahdyeh, N.H. and Hossein, S.K. (2023). Efflux pumps and microbial biofilm formation. Infection, Genetics and Evolution, **112**:105459.

Magill, S.S.; Edwards, J.R.; Bamberg, W.; Beldavs, Z.G.; Dumyati, G.; Kainer, M.A.; Lynfield, R.; Maloney, M.; Mcallister-Hollod, L. and Nadle, J. (2014). Multistate point-prevalence survey of healthcare-associated infections for the emerging infections program healthcare-associated infections and antimicrobial use prevalence survey team. N. Engl. J. Med., **370**:1198-1208.

Meiyazhagan, G.; Raju, R.; Winfred, S.B.; Mannivanan, B.; Bhoopalanm, H.; Shankar, V.; Sekar, S.; Venkatachalam, D.P.; Pitani, R.; Nagendrababu, V.; Thaiman, M.; Devivanayagam, K.; Jayaraman, J.; Ragavachary, R. and Venkatraman, G. (2015). Bioactivity studies of â-lactam derived polycyclic fused pyrroli-dine/pyrrolizidine derivatives in dentistry: *In vitro, in vivo* and *in silico* studies. PLoS One, **10**:e0131433.

Mirghani, R.; Saba, T.; Khaliq, H.; Mitchell, J.; Do, L.; Chambi, L.; Diaz, K.; Kennedy, T.; Alkassab, K.; Huynh, T.; Elmi, M.; Martinez, J.; Sawan, S. and Rijal, G. (2022). Biofilms: Formation, drug resistance and alternatives to conventional approaches. AIMS Microbiol., **8**(3):239-277.

Muthu, D.; Gowri, M.; Suresh, K.G.; Kattimani, V.S. and Girija, E.K. (2019). Repurposing of antidepression drug sertraline for antimicrobial activity against *Staphylococcus aureus*: A potential approach for the treatment of osteomyelitis. New J. Chem., **43**:5315-5324.

Nathan, C. and Cars, O. (2014). Antibiotic resistance-problems, progress, and prospects. N. Engl. J. Med., **371**:1761-1763.

Paes Leme, R.C. and da Silva, R.B. (2021). Antimicrobial activity of non-steroidal anti-inflammatory drugs on biofilm: Current evidence and potential for drug repurposing. Front. Microbiol., **12**:707629.

Poyil, M.M. and Bari, M.D.N. (2023). Repurposing the drug duloxetine for its antibacterial activity against catheter-associated urinary tract infections. The New Armenian Med. J., **17**(1):54-62.

Rai, J.; Randhawa, G.K. and Kaur, M. (2013). Recent advances in antibacterial drugs. Int. J. Appl. Basic. Med. Res., **3**(1):3-10.

Rosa, T.F.D.; Machado, C.S.; Serafin, M.B.; Bottega, A.; Coelho, S.S.; Foletto, V.S.; Rampelotto, R.F.; Lorenzoni, V.V.; Mainardi, A. and Hörner, R. (2021). Repurposing of escitalopram oxalate and clonazepam in combination with ciprofloxacin and sulfamethoxazole-trimethoprim for treatment of multidrug-resistant microorganisms and evaluation of the cleavage capacity of plasmid DNA. Can. J. Microbiol., **67**(8):599-612.

Rukavishnikov, G.; Leonova, L.; Kasyanov, E.; Leonov, V.; Neznanov, N. and Mazo, G. (2023). Antimicrobial activity of antidepressants on normal gut microbiota: Results of the *in vitro* study. Front. Behav. Neurosci., **17**(22):1132127.

Salam, M.A.; Al-Amin, M.Y.; Salam, M.T.; Pawar, J.S.; Akhter, N.; Rabaan, A.A. and Alqumber, M.A.A. (2023). Antimicrobial resistance: A growing serious threat for global public health. Healthcare (Basel)., **11**(13):1946.

Schein, C.H. (2020). Repurposing approved drugs on the pathway to novel therapies. Med. Res. Rev., **40**(2):586-605.

Serwecińska, L. (2020). Antimicrobials and antibiotic-resistant bacteria: A risk to the environment and to public health. *Water.*, **12**(12):3313.

Silva, A.A. L. and Silva, P.M. (2018). Nonantibiotic compounds: The activity of the NSAID diclofenac on bacteria-A review. Int. J. Curr. Microbiol. Appl. Sci., **7**:340–351.

Silver LL. (2011). Challenges of antibacterial discovery. Clin. Microbiol. Rev., **24**(1):71-109.

Steven, M.O. (2016). Non-antibiotic treatments for bacterial diseases in an era of progressive antibiotic resistance. Crit. Care, **20**:397.

Szabó. S.; Feier, B.; Capatina, D.; Tertis, M.; Cristea, C. and Popa, A. (2022). An overview of healthcare-associated infections and their detection methods caused by pathogen bacteria in Romania and Europe. J. Clin. Med., **11**(11):3204.

Valipour, R.; Yilmaz, M.B. and Valipour, E. (2019). Study of DNA-binding activity and antibacterial effect of escitalopram oxalate, an extensively prescribed antidepressant. Drug Res., **69**(10):545-550.

Vidhya, G.; Gowri, M.; Muthu, D.; Sangeetha, K.; Prasath, M.; Govindan, S.K.; Govindan, R.; Vivekanand, S.K. and Girija, E.K. (2022). Repurposing the antibacterial activity of etoposide-A chemotherapeutic drug in combination with eggshell-derived hydroxyapatite. ACS Biomater Sci. Eng., **8**(2):682-693.

Walsh. T.R.; Gales, A.C.; Laxminarayan, R. and Dodd, P.C. (2023). Antimicrobial resistance: Addressing a global threat to humanity. PLoS Med., **20**(7): e1004264.

Ying, L.; Qianqian, Y.; Dan, Z. and Wei, Y. (2021). Mechanisms and control strategies of antibiotic resistance in pathological biofilms. J. Microbiol. Biotechnol., **31**(1):1-7.

Yssel, A.E.J.; Vanderleyden, J. and Steenackers, H.P. (2017). Repurposing of nucleoside- and nucleobase-derivative drugs as antibiotics and biofilm inhibitors. J. Antimicrob. Chemother., **72**:2326-2333.

Citation **Khalid Albasheer, Omer Munder, Albagir Mahdi Ahmed Hassan, Hussein Khalifa and Mohammed H. Karrar Alsharif (2024). Antidepressant drug against bacterial pathogens: Effect of citalopram on biofilm forming hospital-acquired infectious (HAIs) agents. Ann. Phytomed., 13(1):843-849. http://dx.doi.org/10.54085/ap.2024.13.1.89.**