NSAIDs Co-Administration Enhances Antibiotic Susceptibility in MDR *E. coli*: Mechanistic Insights into Cell Membrane Integrity

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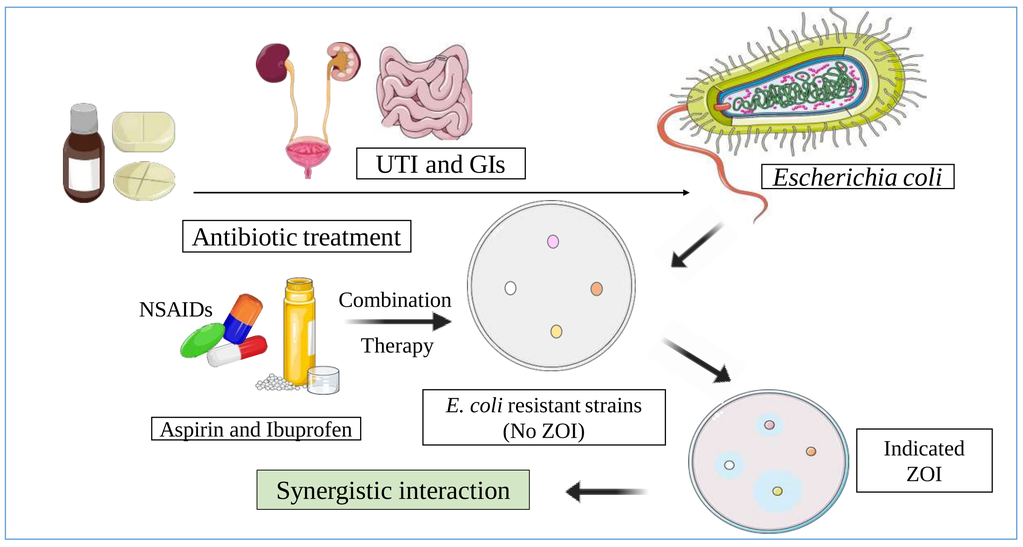
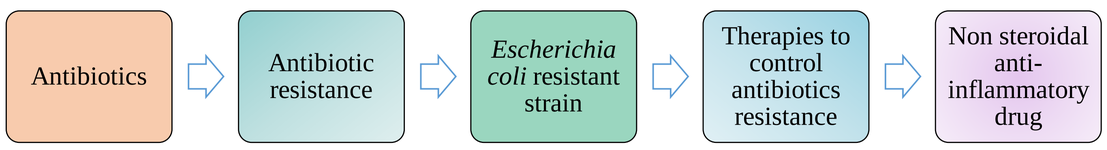
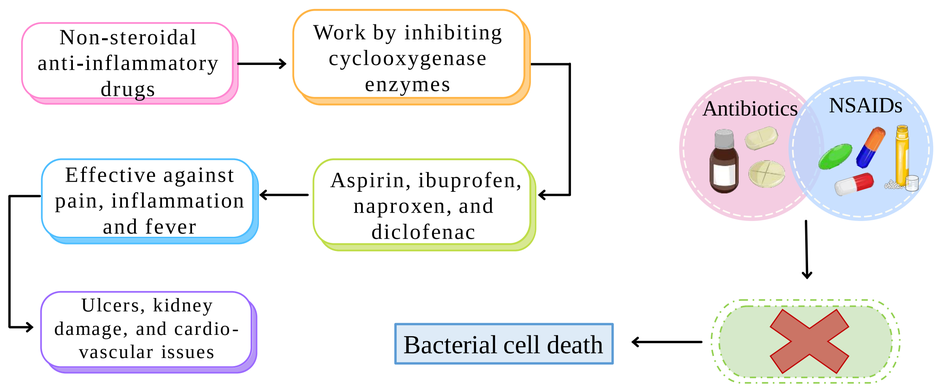
Abstract



Introduction

Antimicrobial resistance is responsible for an estimated **1.27** million deaths annually worldwide.



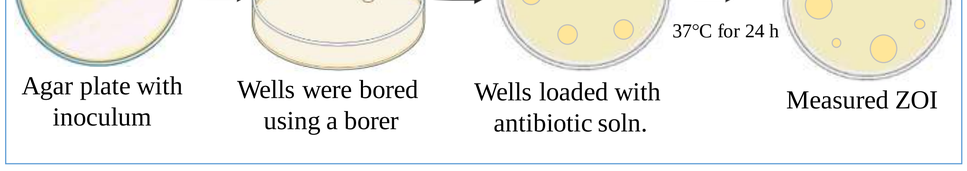


Objectives

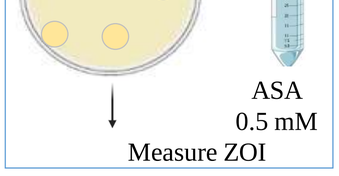
- To investigate whether the combined use results in enhanced or reduced antibiotic resistance in *E. coli*.
- To assess its potential impact on membrane integrity, (nucleic acid and protein stability) etc. in *E. coli*.
- To provide insights into the rational use of NSAIDs and antibiotics in combination in clinical practice to mitigate antibiotic resistance issues.

Materials & Methods

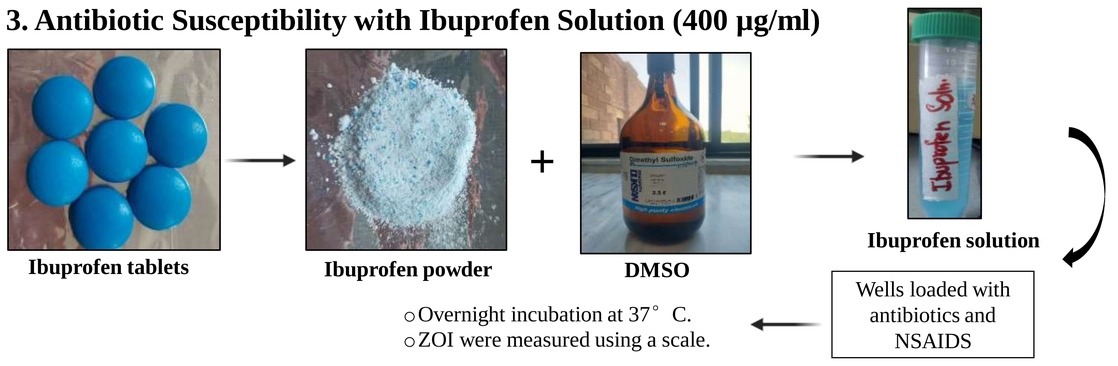
1. Well diffusion method: Co-administering of antibiotics and NSAIDs



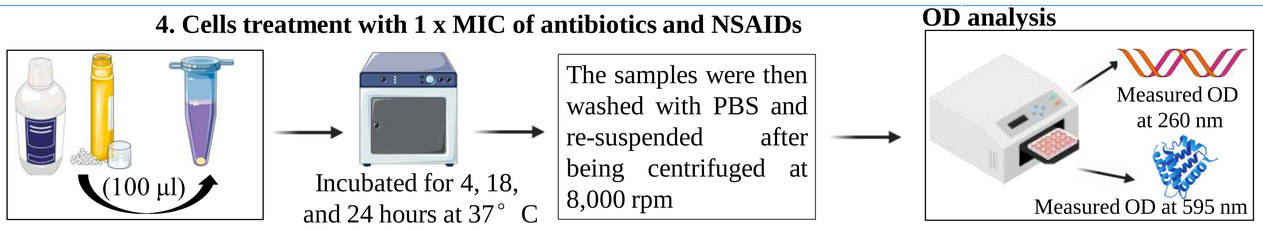
2. Antibiotic wells co-administered with ASA



3. Antibiotic Susceptibility with Ibuprofen Solution (400 µg/ml)



4. Cells treatment with 1 x MIC of antibiotics and NSAIDs



Results & Discussion

Strains were resistant against almost all of the antibiotics and sensitive to only a few antibiotics. But when the synergistic interactions of antibiotics were examined with NSAIDs, most of the resistant strains became sensitive against those antibiotics. Moreover, the changes in the concentrations of proteins and nucleic acids in the extracellular supernatant show that antibiotics and NSAIDs in combination therapy were able to rupture bacterial cell membranes.

Antimicrobial activity of antibiotics in synergy with ASA (0.5 mM)

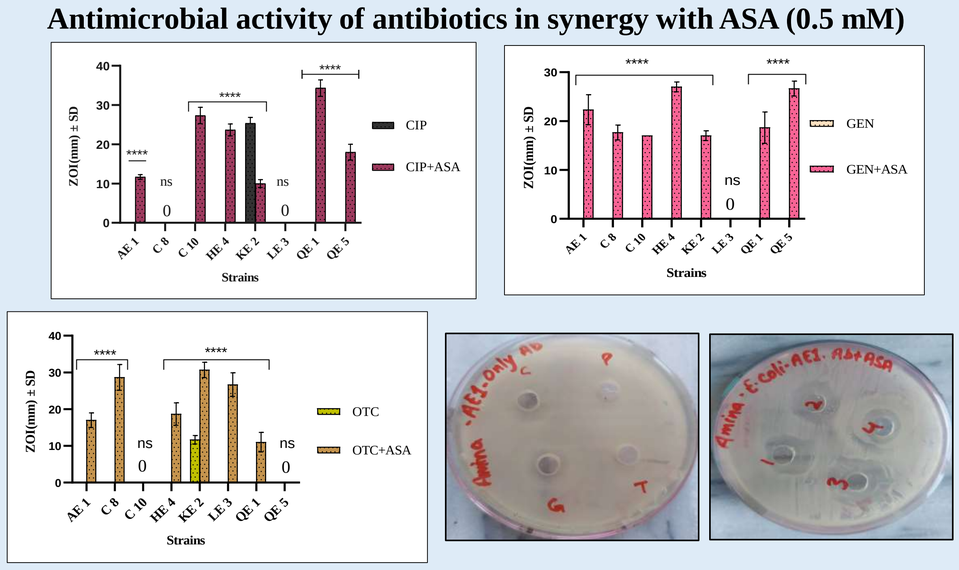


Fig 1. Synergistic effects of CIP (a), GEN (b) and OTC (c) with 0.5 mM ASA on *E. coli* clinical isolates via the Well diffusion test. A significant increase in ZOI indicates a synergistic effect.

Antimicrobial activity of antibiotics in synergy with IBU (400 µg/ml)

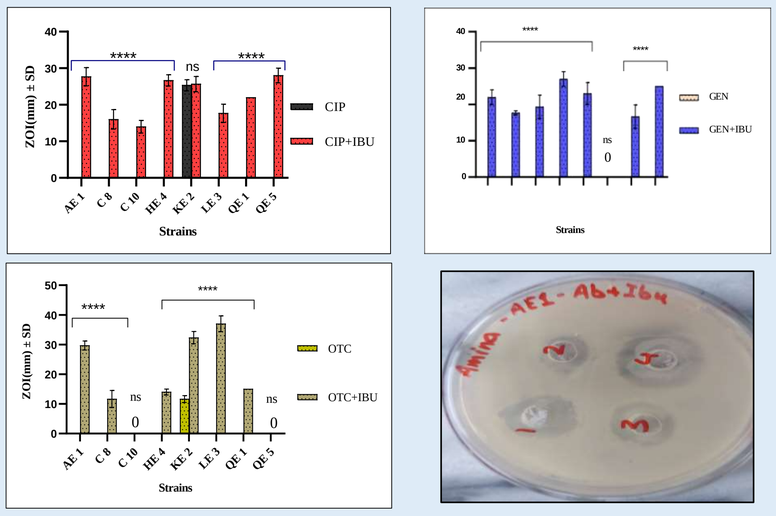


Fig 2. Synergistic effects of CIP (a), GEN (b), OTC (c) and 400 µg/ml IBU on *E. coli* clinical isolates

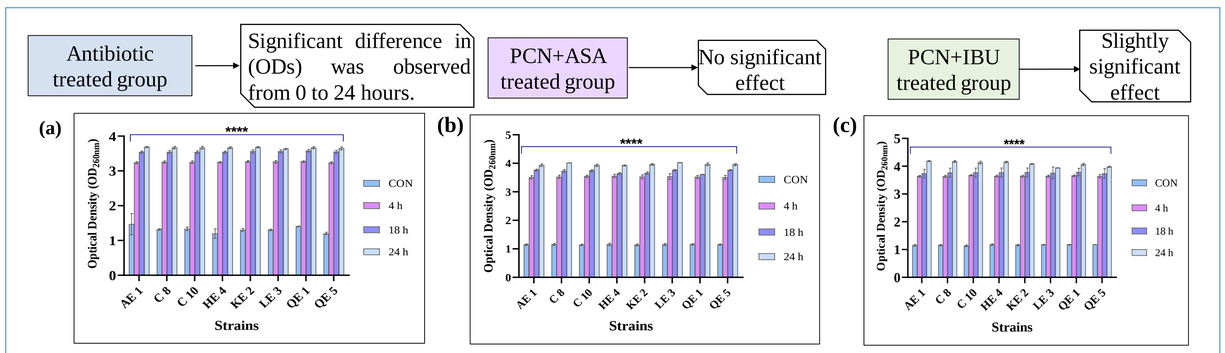


Figure 3. (a) PCN, (b) PCN+ASA and (c) PCN+IBU induced nucleic acid leakage in *E. coli* at 1 X MIC at various time intervals (0 h, 4 h, 18 h, and 24 h).

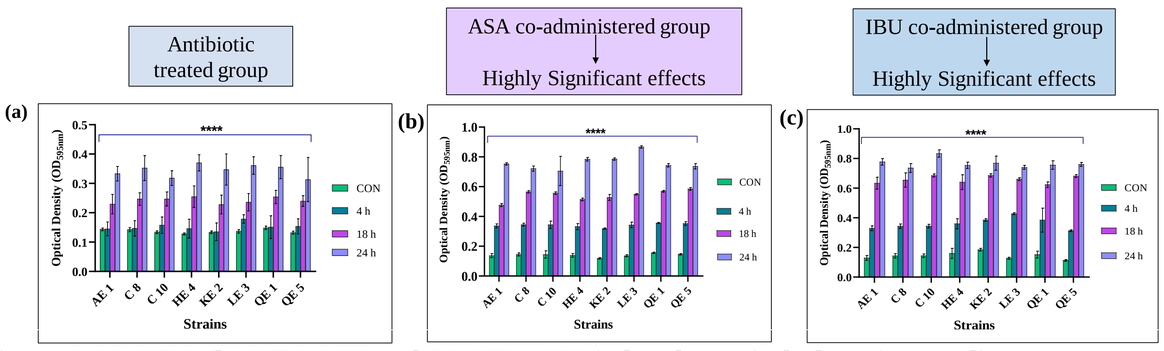


Figure 4. (a) PCN, (b) PCN+ASA and (c) PCN+IBU induced protein leakage in *E. coli* at 1 X MIC at various time intervals (0 h, 4 h, 18 h, and 24 h).

Conclusion

This study has demonstrated the potential of combining antibiotics with NSAIDs to enhance the efficacy of antibiotics against MDR *E. coli* strains. Through a series of assays, our findings indicate that NSAIDs can enhance the effectiveness of antibiotics against multidrug-resistant strains, suggesting their potential as adjunctive agents in addressing bacterial resistance. The results demonstrated enhanced susceptibility and leakage of intracellular components in the presence of NSAIDs in most clinical isolates. These findings propose a promising strategy to address bacterial resistance and improve treatment outcomes for infections caused by *E. coli*.

References

1. Hayat, A., et al. (2025). "Reversion of multidrug resistance in clinical isolates of Escherichia coli using non-steroidal anti-inflammatory drugs (NSAIDs)." The Journal of Antibiotics: 1-12.
2. Liu, Y., et al. (2021). "Reversion of antibiotic resistance in multidrug-resistant pathogens using non-antibiotic pharmaceutical benzydamine." Communications Biology 4(1): 1328.
3. Öztürk, I., et al. (2021). "Nonsteroidal antiinflammatory drugs alter antibiotic susceptibility and expression of virulence-related genes and protein A of Staphylococcus aureus." Turkish journal of medical sciences **51**(2): 835-847.