

# A Permanent Cell Membrane Lesion Causes Benzydamine Bactericidal Effect

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## ABSTRACT

Benzydamine is a pyrozone molecule with anti-inflammatory and antimicrobial effects that is commonly used topically in medicine and veterinary medicine. The antibacterial mechanism of benzydamine was discovered in this work. The antibacterial activity of benzydamine was tested in vitro using the traditional broth microdilution method, and the mechanism of action was discovered using flow cytometry. A total of 120 strains (57 Gram negative bacilli and 63 Gram positive cocci) were chosen from the bacterial collection of the Microbiology Laboratory of Porto, Faculty of Medicine, comprising control ATCC strains and clinical isolates. The tests revealed robust bactericidal efficacy against a wide range of bacteria, including antibiotic-resistant phenotypes such as ESKAPE. (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp.*) In most cases, the least inhibitory concentration was between 100 and 400 g/ml, with Gram-negative bacteria, particularly *Pseudomonas aeruginosa*, requiring greater concentrations. An initial damage of the cell membrane caused the bactericidal action.

**Keywords:** Benzydamine; Bactericidal activity; ESKAPE; Flow cytometry

## INTRODUCTION

Antimicrobial resistance is becoming a global issue, and we may soon find ourselves without the ability to treat infectious infections with conventional treatments. While few new medications are being developed (most of the potential targets have previously been investigated), bacteria develop resistance to new antibiotics quickly. Disinfectants are a critical tool for preventing infection, especially in the face of rising antimicrobial resistance and the emergence of novel pathogens, as is the situation with the current pandemic. Benzydamine is a pyrozone chemical that works by inhibiting the enzyme cyclooxygenase. It has anti-inflammatory and anaesthetic properties. Antimicrobial characteristics, such as antifungal and antibacterial actions, have been described as well. Bacteria can be found in their natural habitats as planktonic cells suspended in a fluid medium; however, bacteria can also thrive by adhering to solid surfaces and producing biofilms. In both phases, bacteria may survive and thrive in a variety of microenvironments, including the oral and vaginal cavities.

## STRAINS

57 Gram-negative bacilli (39 *Enterobacterales*, 10 *Pseudomonas aeruginosa*, and 8 *Acinetobacter baumannii*) and 63 Gram-positive

cocci with varied antimicrobial susceptibility phenotypes were evaluated (23 *Staphylococcus spp* and 40 *Enterococcus spp*). Bacterial strains deposited in the Porto Faculty of Medicine's Microbiology laboratory's clinical strain collection correspond to isolates from a variety of biological products, including blood cultures, bronchial secretions, urine, and wounds. Bacterial strains deposited in the clinical strain collection of the Porto Faculty of Medicine's Microbiology laboratory correspond to isolates from a variety of biological products, including blood cultures, bronchial secretions, urine, and wounds. ESKAPE (*Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp*) bacteria, which are considered the most difficult to treat by the World Health Organization (WHO), were also included in this study.

Flow cytometric assays: A bacterial suspension (0.5 McFarland) was made with each strain, diluted in Muller-Hinton broth and incubated for 1 hour at 35°C with 100, 200, 300, and 400 g/ml of benzydamine and propidium iodide (PI-Sigma Aldrich, St. Louis) a fluorescent probe that can only stain the cells when the cell membrane is permeable, which means a dead cell. Then, using a CytoFLEX, flow cytometric analysis was performed.

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## CONCLUSION

Our findings show that benzydamine has substantial bactericidal activity against a wide range of bacteria, including Enterobacterales (*E. coli*, *Klebsiella*, and *Enterobacter*), *Pseudomonas*, *Acinetobacter*, *Staphylococcus*, and *Enterococcus*. Benzydamine's bactericidal activity against germs including *P. aeruginosa* and *S. aureus* has previously been demonstrated. Apart from its impact as a single medication, the damage of the cell membrane shown here could explain the synergistic effect previously described with benzydamine and antibiotics such as ampicillin, tetracycline, or chloramphenicol. When cells are exposed to benzydamine, their permeability increases, allowing additional chemicals to enter. Even at dosages lower than those employed in anti-inflammatory treatment, benzydamine is a per se potent antibacterial against a wide variety

of species. Our findings show that Gram-positive bacteria have higher activity, which is consistent with a proposed protective effect of Gram-negative bacteria's lipid outer membrane, which limits the access of molecules from the outside. Flow cytometry had already indicated the antifungal impact, as well as the damage of the cell membrane, which was later validated by electron microscopy. In particular, because the cell membrane lesion is a less selective target than traditional antibiotics, it may cause adverse effects in human cells. Nonetheless, topic applications of benzydamine in humans, veterinary medicine, and the clinical environment are of great clinical interest, particularly in light of rising antimicrobial resistance and the need to conserve as many still active antibiotics as possible in order to meet the challenges of One-Health policy.