Investigating the Synergy between Paraben Derivatives and the Antibiotics of Penicillin and Erythromycin

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Abstract

Bacterial resistance has been a threat to our antibiotics, decreasing their effectiveness against many human diseases. In 2010, the World Health Organization made a public call to action urging researchers to find new antibiotics before the year of 2020, showing society's vulnerability to evolving bacterial strains. Thus, it's critical to find an approach to maintaining antibiotic control over bacteria. A current approach has shown that phenolic compounds have proven to work synergistically against bacteria with penicillin and erythromycin antibiotics. In an analogous way, the work herein attempts to use the phenol derivatives known as parabens in combination with the antibiotics penicillin and erythromycin against *S. aureus*. This approach consists of the checkerboard assay by evaluation with the Lorian method to obtain fractional inhibitory concentration (FIC) values. This study concluded that the combination of a polyphenol containing paraben and penicillin and additionally, polyphenol and butyl-iodo parabens with erythromycin showed synergistic effectiveness against *S. Aureus*. Thus, from this research there is potential to further investigate combinations of antibacterial compounds to obtain more effective antibiotics to target emerging strains of resistant bacteria encountered in hospital facilities.

Dedication

My senior honors research thesis is dedicated to

Longwood University's faculty in the chemistry department,

specifically Dr. Andrew Yeagley for allowing me this opportunity to implement lab

techniques and research abilities as an undergraduate and build such

a strong foundation to expand upon within pharmacy school.

Chapter 1: Antibiotics

Bacteria are known to be single-celled living organisms that have an enormous impact in our daily lives, either aiding us, such as the bacteria living on or within our body, or harming us by causing infection. Bacteria are classified as prokaryotes, which contain information in circular units of DNA called plasmids and smaller sections called chromosomes. In addition to a fast replication process leading to quick transfer of their genetic material, bacteria can pass an identical copy of their information within plasmids to other bacterial cells. Antibiotics were created to target harmful strains of bacteria from invading and destroying their host organism, most notably human pathogens.[1]

Using antibiotics to inhibit bacteria from growing is made complicated by the differences between bacterial strains; most important is the variation in their cell wall design. Two known categories are Gram-positive and Gram-negative bacteria shown in Figure 1. Gram-positive bacteria are characterized by a thick cell wall made up of a combination of sugars and peptides called peptidoglycans with an inner cell membrane. Gram-negative bacteria are instead made up of a thin peptidoglycan layer that is located between an inner and outer cell membrane. These cell wall differences influence the effectiveness of antibiotics, as most antibiotics need to cross the bacterial cell wall to prevent bacterial cell functions.[2]

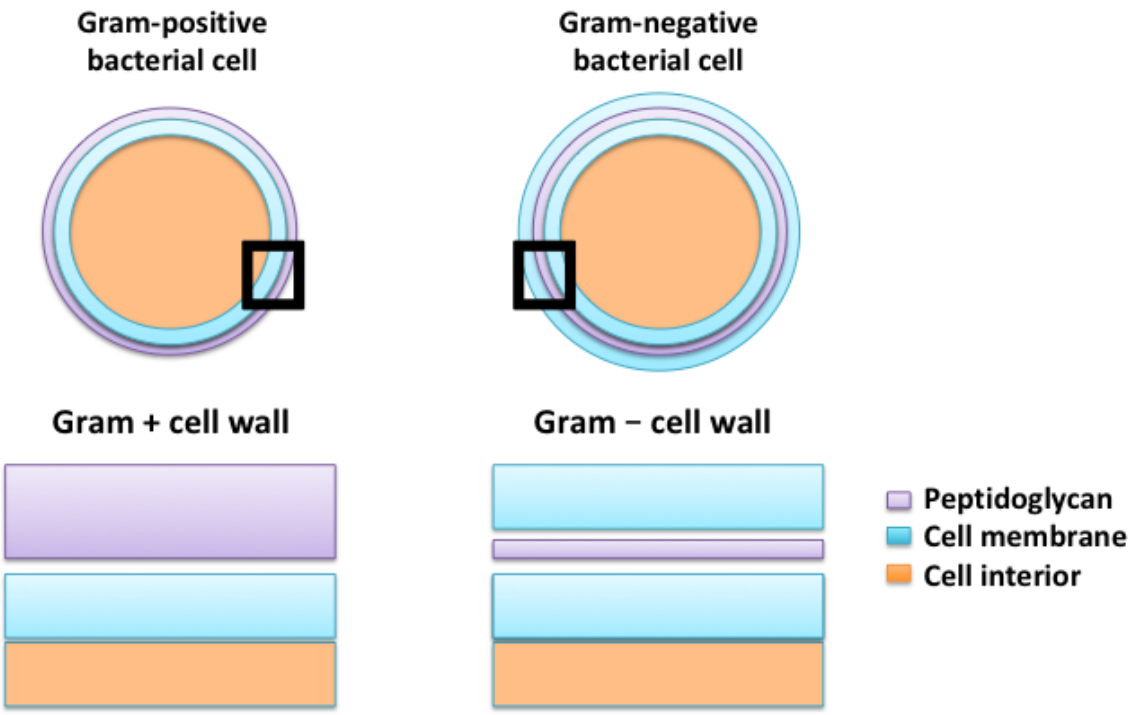

Figure 1: Variations between Gram-positive and Gram-negative bacteria. Gram-positive bacteria are characterized by a thick peptidoglycan wall; Gram-negative bacteria have a thin peptidoglycan wall surrounded by two cell membranes.

Antibiotics are used to prevent bacterial functions such as cell wall synthesis, DNA replication, RNA transcription and protein synthesis. They are classified into two categories of bactericidal and bacteriostatic depending on the mechanism of preventing bacterial growth. Bactericidal antibiotics are known to cause bacterial cell death. Bacteriostatic antibiotics inhibit the growth of bacteria, allowing the bacteria to remain in a stationary phase of growth, and thus do not result in cell death. With bacteriostatic mechanisms, removal of the bacteria requires some other mechanism of cell death, such as a healthy immune system.[3]

The two types of antibiotics employ different mechanisms when preventing bacterial growth. Bactericidal antibiotics are typically small organic molecules that can depolarize the cell membrane, prevent cell wall synthesis, inhibit DNA synthesis, or increase membrane fluidity, which is shown in Figure 2. The commonly known penicillin antibiotic is an example of a bactericidal antibiotic. Bacteriostatic antibiotics work primarily by targeting mechanisms including DNA replication, disrupting protein synthesis, and slowing or inhibiting cellular metabolism. Many of these targets are components of the central dogma of molecular biology, which is shown in Figure 3. A common example of a bacteriostatic antibiotic that works by inhibiting protein synthesis is **a.** **b.** **c.**

erythromycin. It is possible, however, for bacteriostatic antibiotics to lead to bactericidal action at higher concentrations; this is also true for erythromycin.

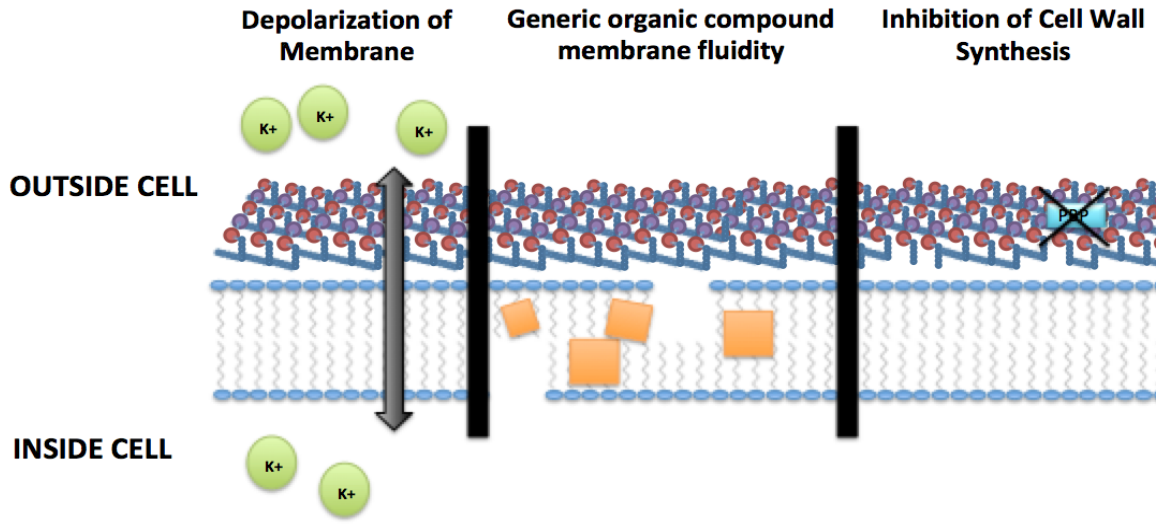

Figure 2: Bactericidal mechanisms acting on the cell membrane. **These mechanisms include a) depolarization of the membrane, b) generic organic compounds affecting membrane fluidity, and c) disruption of the cell wall synthesis.**

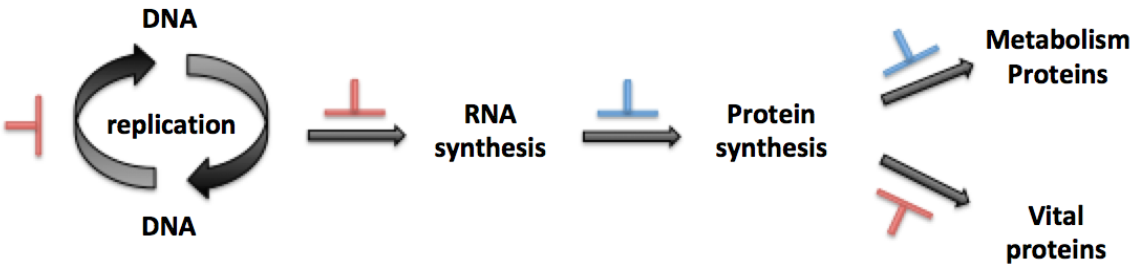

Figure 3: Small molecule targets within the central dogma of molecular biology. **Bacteriostatic mechanisms work by prevention of protein synthesis, which could work by way of preventing previous steps in both inhibiting DNA synthesis and RNA synthesis. Red inhibition is by bactericidal mechanism; Blue inhibition is by bacteriostatic mechanism.**

For this study, penicillin was used as a representative bactericidal antibiotic. Penicillin is one of the oldest known antibiotics belonging to the beta-lactam family,

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