GESM Chemistry Journal "The Chemist's Digest"
2nd Article

Combination Drug Therapy

What is combination drug therapy?

Combination drug therapy uses drugs together to enhance the drug's effectiveness (TuftsNow, 2022). Alternatively, it utilizes antibiotics combined with inhibitors (Si et al., 2023).

There are several reasons for the usage of combination drug therapy. Firstly, we have to consider that bacteria exist in different states and that there are different kinds of cells in a tumor. Thus, diseases may have different causes and more than one type of infection must be treated. Such infections are called heterogeneous. For instance, one drug may combat against bacteria in specific states, so another drug is required to target the other bacteria subpopulations or the so-called persister cells. Another reason to use combination drug therapy is to slow the development of drug resistance. Monotherapy, on the other hand, may lead to faster formation of resistance. However, not all combination drug therapy decreases the acquisition of drug resistance and some might even promote resistance. Thus, more research is required in this field. In some cases, the drugs applied may improve each others' effectiveness. This is called synergy. (TuftsNow, 2022)

Drug combination therapy is more convenient and effective for patients than monotherapy for various reasons. With fewer medications required in a day, patients are more likely to follow their medical routine compared to them needing multiple medications throughout the day. Fewer medications may also reduce their overall cost along with reduced chance of getting the wrong medication. Combination drugs also contain fewer dosages of each component, which may lead to fewer side effects compared to a higher dosage of only one certain component (Terrie, 2010).

Aside from the general conveniences, combination drug therapy is also more practical for various treatments such as for hypertension, diabetes, Alzheimer's disease, breast cancer, and arthritis. Many patients with hypertension require more than one drug for effectiveness, and there is better glycemic control in diabetic patients when drugs work at two different sites. For Alzhemer's disease, a clinical trial published in the Journal of the American Medical Association showed that a combination of the N-methyl-D-aspartic acid receptor antagonist, memantine hydrochloride, and the cholinesterase inhibitor, donepezil proved to me more useful in reducing cognitive decline compared to just taking donepezil (Terrie, 2010).

However, certain concerns also arise taking into account that combination drugs are in fixed doses, which may prove to be a disadvantage. Altering doses of drugs may be difficult since they are only available in certain ratios, and it may not fit each person's treatment. This can also lead to unnecessary dosage of a component that is not needed. This luckily is being explored further to make more dosage combinations available, which may soon prevent any unnecessary medication. It is also a thing to note that drug combinations need to be tested to see how they react to each other, to see if they carry out their functions successfully, without hindering the functionality of any other drug. (Terrie, 2010)

Today, numerous disease treatments use combination drug therapy. Examples include tuberculosis, HIV, and various kinds of cancer (TuftsNow, 2022).

Examples of antibiotics combinations and their effects

By targeting different bacterial processes or by protecting each other from enzymatic degradation, antibiotic combinations can lead to improved outcomes in the treatment of various infections. Examples of antibiotic combinations include, Penicillin and Streptomycin, Amoxicillin and Clavulanate (Augmentin), and Trimethoprim and Sulfamethoxazole (Bactrim, Septra). These examples highlight the chemical basis and advantages of combination therapy in addressing the challenge of antibiotic resistance.

Penicillin and Streptomycin are commonly used together in cell culture to determine the physiology and biochemistry of cells (Thermo Fisher Scientific, n.d.). According to the National Library of Medicine, (n.d.), antibiotics minimize the loss of valuable cells, reagents, and time due to contamination during cell culture. The combination maintains an aseptic environment essential to maintaining the structure and composition of cells.

The combination of Amoxicillin and Clavulanate (a combination otherwise known as *Augmentin*) is used to treat bacterial infections. This dual-drug approach works because while antibiotics like Amoxicillin work against gram-positive bacteria, they struggle to penetrate the cell walls of gram-negative bacteria. So while antibiotics are able to treat gram-positive bacteria, an additional drug must be used for gram-negative bacteria. In this case, the drug used is clavulanate acid or *Clavulanate*. It is used because it increases the spectrum to include beta-lactamase-producing strains (Evans et al., 2023) that prevents bacteria from destroying Amoxicillin (National Library of Medicine, n.d.). Together, the drugs are known as "Augmentin" and stop infectious bacteria from producing the enzymes that make them more resistant to antibiotics (Johnson, 2023).

Image 1: *Augmentin Tablet (Ghose, 2017)*

Lastly, Trimethoprim and Sulfamethoxazole. This combination is used to treat infections synergistically in order to stop bacterial folate metabolism (Werth, 2024). According to Kemnic (2022), Trimethoprim and Sulfamethoxazole are competitors of dihydrofolate reductase and p-aminobenzoic acid (PABA). Combined, they halt the production of folate and inhibit dihydropteroate synthase.

Combining Antibiotics with Adjuvant Molecules

Combining antibiotics with adjuvant molecules can play an important role in modern medicine, as it enhances the efficacy of antibiotics, targets resistance mechanisms, and reduces negative side effects upon consumption. These adjuvant molecules were created to increase antibacterial activity and therefore the effectiveness of drug therapy. Bacteria's defense mechanisms can be inhibited via both β-lactamase and efflux pump inhibitors. β-lactamase inhibitors inhibit β-lactamase enzymes produced by bacteria that degrade β-lactam antibiotics, whereas efflux pump inhibitors block efflux pumps that bacteria use to expel antibiotics from their cells, thereby increasing the intracellular concentration of the antibiotic (Si et al., 2023).

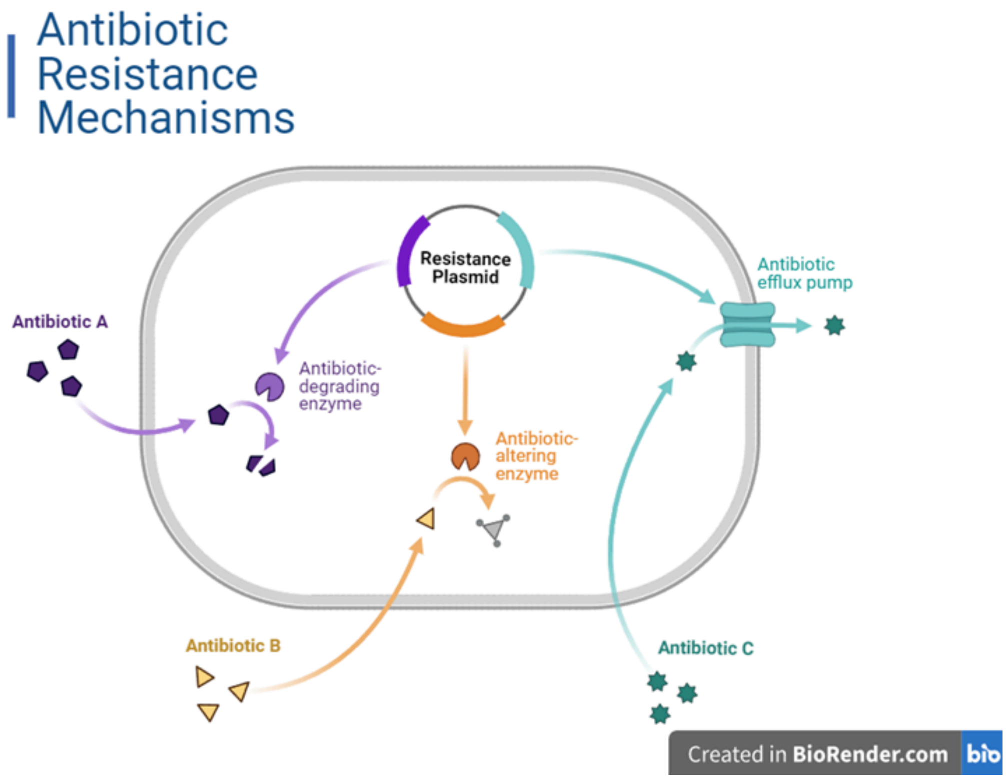
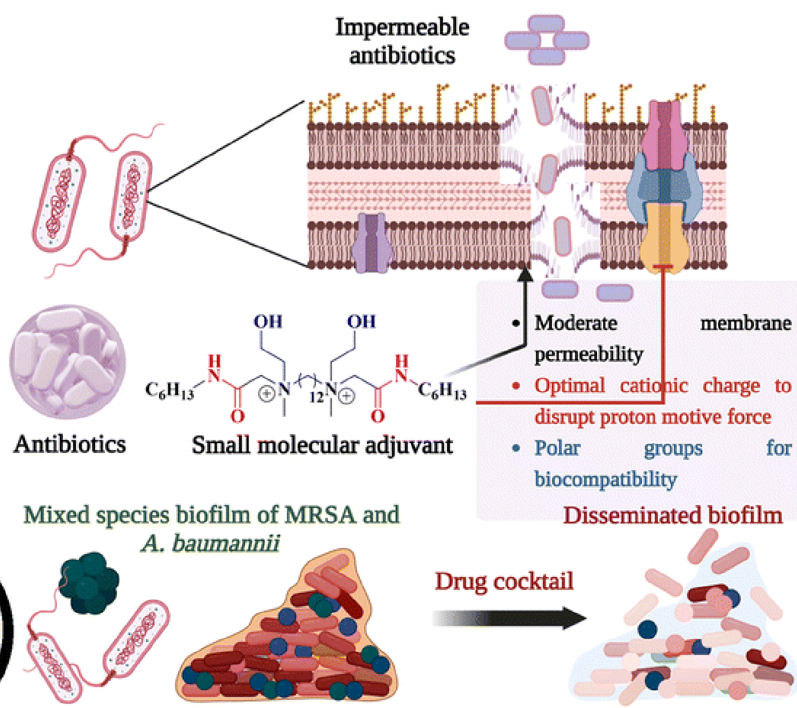


Image 2: *Highlighting the Relationship of Efflux Pump and Antibiotics (Barron, 2023)*



PICK OF THE WEEK

Image 3: *Adjuvant Combination Disrupting Multispecies Biofilm (Dey et al., 2024)*

Adjuvant molecules also disrupt biofilms, which are protective layers formed by bacterial communities, making bacteria more susceptible to treatment. Some adjuvants interfere with quorum sensing, a process by which bacteria communicate and coordinate activities such as virulence and biofilm formation. This can reduce the overall pathogenicity of bacterial infections. Combining antibiotics with adjuvants enhances efficacy by boosting the antibacterial activity of antibiotics, which allows lower doses of drugs to be used for the same effect. This reduced dosage leads to less toxicity and fewer side effects. Additionally, adjuvants can directly inhibit bacterial resistance mechanisms, thereby slowing the development of resistance and making antibiotics more effective in treating chronic infections and cases where single-drug therapies fail due to resistance (Si et al., 2023).

However, there are potential challenges to this approach. Bacteria may develop resistance to the adjuvants themselves, similar to how they develop resistance to antibiotics. This potential for resistance necessitates ongoing research and development to identify new adjuvant molecules and understand their mechanisms of action. Moreover, ensuring that adjuvants do not introduce new side effects or safety issues is crucial, as these could potentially make infections harder to treat. The research and approval process for new antibiotic-adjuvant combinations is often lengthy and expensive, which adds to the complexity of developing these therapies.

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