Understanding the Synergy Between Antibiotics and Phenolic Acids

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Before the discovery of antibiotics, bacterial infections constituted a leading cause of human mortality. Antibiotics used during World War One and the subsequent introduction of penicillin as the first therapeutic agent ended that era. Yet, the rise of antimicrobial resistance (AMR) and multi-drug resistance (MDR) now threatens to render current treatments ineffective. Although new antibiotic classes have been developed to address AMR infections, devising entirely novel drugs has become increasingly difficult due to limited cellular target in bacterial cell. One promising strategy involves using adjuvants that sensitize AMR bacteria to existing antibiotics. I hypothesized that dietary polyphenols, once metabolized by gut microbiota, yield phenolic acids with increased antimicrobial activity. My previous research revealed a strong combinatorial effect between phenolic acid dihydroxybenzoic acid (DHBA) and various antibiotics. The present study demonstrates the antibiotic-adjuvant activity of DHBA and Colistin (a last resort antibiotic) combination against Gram-negative AMR bacteria and showed minimal perturbation of the gut microbiome. Mechanistic analyses using a large collection of Escherichia coli gene mutants showed that, although DHBA and colistin share some targets, DHBA exerts broader activity. This extensive target range impedes the emergence of AMR, thereby enhancing the efficacy of last-resort antibiotics. By leveraging the synergy between DHBA and existing antibiotics, this approach augments current therapies and helps mitigate increasing AMR challenges. These findings underscore the potential of phenolic acids as antibiotic enhancers, diminishing the likelihood of resistance development and introducing new paradigms for combating life-threatening infections.

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