## Enhancement of Beta-lactam Antibiotic Susceptibility by Tannic Acid through Beta-lactamase Inhibition

Kim, Justin

Beta-lactamase hydrolyzes beta-lactam antibiotics, making antibiotic treatment of bacterial infections ineffective. An emerging beta-lactamase, carbapenemase, can even hydrolyze last resort antibiotics, carbapenems. Efficacy of antibiotic treatment with existing beta-lactam antibiotics may be substantially improved by combined use with beta-lactamase inhibitors. Unfortunately, beta-lactam rings contained in most beta-lactamase inhibitors make these inhibitors susceptible to hydrolysis by carbapenemase. The purpose of this study was to evaluate the effect of a safe, natural, non-beta-lactam polyphenol, tannic acid, on bacterial antibiotic susceptibility. In this study, Escherichia coli producing class A TEM-1 beta-lactamase was used as a model bacterium. Antibiotic susceptibility tests demonstrated that tannic acid lowered the minimum bactericidal concentrations (MBCs) of two beta-lactam antibiotics, carbenicillin and ampicillin, by >8-fold. An enzyme assay using a UV/VIS spectrophotometer indicated that tannic acid inhibited TEM-1 beta-lactamase inhibitor clavulanate (p=0.88). In addition, binding between tannic acid and TEM-1 beta-lactamase was confirmed by intrinsic fluorescence assays (p<0.01). Computational modeling using SwissDock suggested strong and highly probable binding of tannic acid to active sites of not only TEM-1 beta-lactamase, but also its homologue, KPC-2 carbapenemase. The computational results hold high promise of tannic acid as a potential non-beta-lactam inhibitor for carbapenemases. Further investigations with carbapenemase producing bacteria will be required to verify clinical relevance of tannic acid.

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