RESCON 2025 LS 24

IN SILICO DRUG DISCOVERY OF FLUOROQUINOLONE-LIKE COMPOUNDS FROM PHYTOCHEMICALS

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Fluoroquinolones are broad-spectrum antibiotics with rising rates of resistance. They are commonly used to treat pneumonia, urinary tract infections, gastroenteritis, and gonococcal infections. Prescription is restricted due to the increased risk of rare, significant adverse events. The discovery of novel drug alternatives is a promising strategy to overcome these challenges. Phytochemicals are gaining increased scientific attention due to their favorable attributes as antimicrobials. The core purposes of the research were to develop a Machine Learning (ML) pipeline using Konstanz Information Miner (KNIME) to discover potential phytochemicals with fluoroquinolone-like properties and evaluate their drug-likeness based on Lipinski's rule of five. In this study**,** KNIME version 4.7.7 was used together with the RDKit community node library. Structural data were acquired for 20 fluoroquinolone antibiotics, 20 non-antibiotic drugs, and 401 phytochemicals from ChEMBL, in Simplified Molecular Input Line Entry System (SMILES) format. The RDKit Fingerprint node was used to generate MACCS fingerprints, and then data were prepared for ML. Artificial Neural Network (ANN), Random Forest (RF), and Support Vector Machine (SVM) algorithms were trained on the filtered ChEMBL dataset to discriminate active compounds from inactive ones. ML models achieved overall prediction accuracies of 98.9%, 99.5%, and 88.2%, respectively, in predicting fluoroquinolone-like phytochemicals. Based on structural similarities, the algorithms identified 3 (ANN) and 34 (SVM) phytochemicals as potential fluoroquinolone-like candidates. The three ANN-predicted phytochemicals, such as neocryptolepine, deschloroelatol, and elatol represent the most promising alternatives for further analysis. Predicted molecules were filtered with Lipinski's rule of five. Thirty-five phytochemicals can be used as orally active drugs from the predicted hits. However, further *in vitro* and *in vivo* efficacy evaluations need to be conducted on these phytochemicals to confirm their potential to discover novel fluoroquinolones. As future directions, candidate compounds will be screened using the 96-well plate method.

Keywords: Antimicrobial resistance, Drug discovery, Fluoroquinolones, KNIME, Machine Learning