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NOVEL DRUG COMBINATIONS AGAINST METHICILLIN RESISTANT *Staphylococcus aureus*

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Methicillin-resistant *Staphylococcus aureus* (MRSA) causes a major public health issue due to its resistance to multiple antibiotics, leading to severe infections and increased healthcare costs. As traditional treatments are becoming less effective against antibiotic-resistant bacteria like MRSA, innovative therapeutic approaches are necessary. In many reported cases, synergistic drug combinations have been used to address issues related to antibiotic resistance. Therefore, this study aimed to identify novel synergistic drug combinations to combat MRSA by predicting the bioactivity of 3000 drug candidates, primarily phytochemicals. Using the KNIME Analytics Platform, an *in-silico* screening pipeline was developed to predict the activity of these phytochemicals against MRSA. The study retrieved 2D structural information of the 3000 drug candidates, 25 antibiotics, and 17 drug combinations from the ChEMBL database. The training data were selected from current treatment practices in hospitals, while test data were chosen based on literature on antimicrobial properties. Cheminformatics tools and machine learning models, including Random Forest (RF), Artificial Neural Network (ANN), and Support Vector Machine (SVM), were used to train and validate the data. Model performances were evaluated using accuracy, Root Mean Squared Error (RMSE), precision, recall, F1 score, and Cohen's kappa. Synergistic drug combinations were predicted with accuracies of 98.41% for RF, 98.01% for ANN, and 98.21% for SVM. Five compounds: Psoralen, Nintedanib, Deuxibuprofen, D-Pinitol, and Gallic acid were identified as promising candidates against MRSA after filtering through a Pan-assay. These compounds possess known antimicrobial properties but are not commonly used against MRSA. The drug combination of CHEMBL235842 and CHEMBL2152348 demonstrated the highest synergy score, suggesting that combining these compounds could target more bacterial survival pathways than single-drug therapies, reducing resistance development. This research developed a Machine learning pipeline to predict drug synergy, reducing the experimental sample size and saving resources and time for *in-vitro* experiments.

Keywords: Antibiotic resistance, KNIME, MRSA, Machine learning, Synergy prediction