Novel Prediction of Adverse Drug Reactions and Underlying Pathological Mechanisms via Hierarchical Classification

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Adverse drug reactions (ADRs) represent a significant threat to public health, causing an estimated 100,000 deaths annually in the U.S., but accurate predictions of ADRs caused by drug-drug interactions (DDIs) and underlying pathological mechanisms need clarification. This study's objective was to create a computational model to predict DDI-associated ADRs and pathological mechanisms for any drug co-administration. A hierarchical model consisting of Random Forest Classifiers and a Support Vector Machine was developed using drugs' chemical fingerprints to predict target, enzyme, and transporter (TET) profiles, which were then utilized to predict ADRs, achieving an overall accuracy of 91%. The robustness of the integrative model was further tested and validated for DDIs involving three widely prescribed drugs: levothyroxine, omeprazole, and atorvastatin. Alterations of TET interactions in drugs' pharmacological profiles successfully identified targets, enzymes, and transporters critical in DDIs associated with the three drugs. Pathway analyses of bleeding, platelet inhibition, and myopathy around the respective key molecules provided mechanisms responsible for the DDI-associated ADRs, which were supported by literature. Unexplored ADRs were also investigated for DDIs using the model. For the ADR of interstitial lung disease (ILD), the model unveiled key molecules and potential pathways underlying atorvastatin mediated DDIs. Overall, this study presents a novel model that can predict ADRs and elucidate their pathological mechanisms, which can be enhanced with regressors to better describe the variations of ADR risks. The model can also be applied to analyze DDI-associated ADRs of drugs under development in advance, paving the way for greater drug safety.

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