Breaking New Ground in Phenotyping: Solanidine Metabolism as a CYP2D6 Activity Indicator

CYP2D6 metabolizes 20–30% of clinically used drugs, including antidepressants, beta-blockers (e.g., metoprolol), and prodrugs like tamoxifen and codeine. Its broad genetic variability results in metabolic differences from poor to ultra-rapid metabolizers, affecting drug efficacy and safety. However, genotyping alone cannot fully predict CYP2D6 activity due to non-genetic factors, highlighting the need for precise phenotyping methods. The administration of an external probe drug is impractical and carries the risk of adverse effects in many clinical situations. It would be of value to validate biomarkers that can be analyzed in plasma or urine of patients without external administration of CYP2D6 probe drugs.

Recent works employing untargeted metabolomics have identified solanidine, a naturally occurring steroidal alkaloid found in potatoes, along with its metabolites—3,4-seco-solanidine-3,4-dioic acid (SSDA) and 4-OH-solanidine—as potential biomarkers of CYP2D6 activity in human urine. These findings support a minimally invasive approach to evaluating CYP2D6 function in biofluids. Previous studies involving genotyped patients have further validated the plasma SSDA/solanidine and 4-OH-solanidine/solanidine ratios as dietary-derived markers of CYP2D6 activity.

The proposed master's thesis project aims to develop a precise quantification method for solanidine and its metabolites in human serum, plasma, and urine, enabling their potential use as a clinical tool. Due to the unavailability of chemical standards for solanidine metabolites, our current focus is on isolating and purifying these metabolites from urine to obtain highly pure compounds for accurate quantification. This project offers the master's student a unique opportunity to contribute to the development of a specialized phenotyping tool with potential clinical applications. Through this work, the student will gain a solid foundation in drug metabolism and phenotyping, along with hands-on experience in developing and validating bioanalytical methods for small-molecule quantification using LC-MS/MS.

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