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Prediction of Drug-Drug Interaction Due to the Inhibition of Specific Intestinal Drug-Metabolizing Enzymes by Celastrol

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SUMMARY. **Intestine is an important barrier for limiting the absorption of drugs through oral administration. Inhibition of drug-metabolizing enzymes (DMEs) in the intestine can induce severe drug-drug interaction. Given that celastrol is being developed for its multiple clinical application, the present study aims to investigate the inhibitory potential of celastrol towards two important UDP-glucuronosyltransferases (UGTs) isoforms UGT1A8 and UGT1A10, which are highly expressed in the intestine. Recombinant UGT1A8 and 1A10-catalyzed 4-methylumbelliferone (4-MU) glucuronidation reaction was utilized as the probe reaction for evaluating the celastrol's inhibition towards UGT1A8 and UGT1A10. Data analysis using Dixon and Lineweaver-Burk equations showed that celastrol competitively inhibited the UGT1A8 activity, and noncompetitively inhibited the activity of UGT1A10. The inhibition kinetic parameters (K_i) were calculated to be 0.6 μM and 0.6 μM for UGT1A8 and UGT1A10, respectively. Using the anti-tumor therapeutic concentration (1-10 μM), the area under the curve (AUC) of plasma concentration-time course was predicted to increase 67 %-15.7-fold for co-administered drugs mainly undergoing UGT1A8, 1A10-catalyzed metabolism. This information is beneficial for the research and development of celastrol as a promising drug.**

KEY WORDS: Celastrol, Intestine, Research and development.

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