Evaluation of Inhibition of UDP-Glucuronosyltransferase (UGT) 1A1 by Demethylzeylasteral

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SUMMARY. Many severe clinical adverse effects can be induced through inhibition of UDP-glucuronosyltransferase (UGT) 1A1, including clinical drug-drug interactions (DDI) and metabolic disorders of endogenous substances. The present study aims to investigate the inhibition of UGT1A1 by demethylzeylasteral which is an important bioactive component isolated from Tripterygium wilfordii Hook F. Recombinant UGT1A1 was used as enzyme source, and 4-methylumbelliferone (4-MU) was employed as probe substrate. The results showed that the residual activity of 4-MU glucuronidation was 8.5 ± 1.1 % of the control activity at 100 μM of demethylzeylasteral for UGT1A1. Furthermore, inhibition kinetic type and parameters were evaluated. Dixon plot and Lineweaver-Burk plot showed that demethylzeylasteral non-competitively inhibited UGT1A1, and the inhibition parameter (Ki) was determined to be 21.7 μM for UGT1A1. This kind of inhibitory effect need much attention when demethylzeylasteral and demethylzeylasteral-containing herbs (e.g. Tripterygium wilfordii Hook F.) were co-administered with the drugs mainly undergoing UGT1A1-catalyzed metabolism.

KEY WORDS: Demethylzeylasteral, Drug-drug interaction, UDP-glucuronosyltransferase (UGT) 1A1.

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