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Evaluation of the Interaction Between UDP-Glucuronosyltransferases (UGTs) and Aurantio-Obtusin

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SUMMARY. **The present study aims to investigate the inhibition of aurantio-obtusin and glucoaurantio-obtusin towards important UDP-glucuronosyltransferases (UGTs) isoforms in liver and intestine. Various UGT isoforms-catalyzed 4-methylumbelliferone (4-MU) glucuronidation reaction was used as the probe reaction. Initial screening of the inhibitory potential at 100 μM of aurantio-obtusin and glucoaurantio-obtusin showed that aurantio-obtusin exhibited stronger inhibition towards all the tested UGT isoforms than glucoaurantio-obtusin, indicating the important role of deglycosylation process towards the inhibition potential towards UGT isoforms. The inhibition kinetic type and parameters were determined for the UGT isoforms which activities were inhibited more than 80%, including UGT1A1, 1A3, 1A9, and 1A10. Dixon and Lineweaver-Burk plots demonstrated that aurantio-obtusin noncompetitively inhibit the activity of UGT1A1, 1A9, and 1A10, and competitively inhibit the activity of UGT1A3. The inhibition kinetic parameters were calculated to be 1.3, 11.2, 3.3, and 8.6 μM for UGT1A1, 1A3, 1A9 and 1A10, respectively. All these results indicated the possible herb-drug interaction between aurantio-obtusin or glucoaurantio-obtusin containing herbs and clinical drugs mainly undergoing UGT1A1, 1A3, 1A9 or 1A10-catalyzed metabolic elimination.**

RESUMEN. El presente estudio tiene como objetivo investigar la inhibición de aurantio-obtusina y glucoaurantio-obtusina sobre importantes isoformas de UDP-glucuronosiltransferasas (UGTs) en hígado e intestino. Varias isoformas de UGT 4- metilumbeliferona (4-MU) que catalizan reacciones de glucuronidación se utilizaron como sonda de reacción. Los ensayos iniciales del potencial inhibitorio de aurantio-obtusina y glucoaurantio-obtusina 100 μM mostró que aurantio-obtusina exhibió una inhibición más fuerte hacia todas las isoformas de UGT probadas que glucoaurantio-obtusina, lo que indica el importante papel de proceso de deglicosilación en relación al potencial de inhibición sobre isoformas de UGT. Se determinaron el tipo y los parámetros de cinética de inhibición para las isoformas de UGT que inhibieron más del 80 %, incluyendo UGT1A1, 1A3, 1A9 y 1A10. Los gráficos de Dixon y Lineweaver-Burk demostraron que aurantio-obtusina inhibe no-competitivamente la actividad de UGT1A1, 1A9 y 1A10 e inhibe competitivamente la actividad de UGT1A3. Los parámetros cinéticos de inhibición se calcularon en 1,3, 11,2, 3,3 y 8,6 M para UGT1A1, 1A3, 1A9 y 1A10, respectivamente. Todos estos resultados indican la posible interacción de hierbas que contienen aurantio-obtusina o glucoaurantio-obtusina con fármacos clínicos, afectando principalmente la eliminación metabólica catalizada por UGT1A1, 1A3, 1A9 o 1A10.

KEY WORDS: Aurantio-obtusin, Glucoaurantio-obtusin, Herb-drug interaction, UDP-glucuronosyltransferases (UGTs).

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