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In vitro Characterization of the Intestinal Absorption Mechanism of Dihydromyricetin in Caco-2 Cell Model

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***SUMMARY*. Dihydromyricetin possesses numerous biological and pharmacological activities, and However, little data is available for its intestinal absorption mechanism. This study investigates the intestinal absorption characteristics of dihydromyricetin using Caco-2 cell transwell model. The intestinal absorption characteristics of dihydromyricetin was investigated using Caco-2 cell transwell model. Then, the effects of time (30, 60, 90, and 120 min), concentration (2, 10, and 20 μM), temperature (37 or 4 °C), paracellular pathways, and efflux transporters inhibitors (verapamil, cyclosporin A, MK-571, and reserpine) on transport of dihydromyricetin were investigated. The Papp values from BL-AP of dihydromyricetin are much higher than the AP-BL permeability. The results indicated that the intestinal transport of dihydromyricetin was a time- and concentration-dependent active transport. Opening of cell junctions brings little influence in dihydromyricetin permeability in both directions, which indicated that the paracellular pathway was not involved in transport of dihydromyricetin. Decrease in the Papp(BL-AP) at 4 °C with respect to the Papp(BL-AP) at 37 °C indicate that the efflux of dihydromyricetin was energy dependent transport. Both verapamil and cyclosporin A could increase the Papp(AP-BL) and decrease the Papp(BL-AP) value. However, MK571 or reserpine have no obvious effects on the transport of dihydromyricetin. These results indicated that dihydromyricetin might be a substrate of P-gp, and while not a substrate of BCRP and MRP2. P-gp was involved in transport of dihydromyricetin, which hindered the absorption of dihydromyricetin in intestine, and drug-drug interaction might be occurred when dihydromyricetin was co-administrated with P-gp inhibitors.**

RESUMEN. La dihidromiricetina posee numerosas actividades biológicas y farmacológicas y, sin embargo, hay pocos datos disponibles sobre su mecanismo de absorción intestinal. Este estudio investiga las características de absorción intestinal de la dihidromiricetina usando el modelo de transwell de células Caco-2. Las características de absorción intestinal de dihidromiricetina se investigaron utilizando el modelo de transwell de células Caco-2. Luego fueron investigdos los efectos del tiempo (30, 60, 90 y 120 min), la concentración (2, 10 y 20 μM), la temperatura (37 o 4 ° C), las vías paracelulares y los inhibidores de los transportadores de salida (verapamilo, ciclosporina A, MK-571 y reserpina) en el transporte de dihidromiricetina. Los valores de Papp de BL-AP de dihidromiricetina son mucho más altos que la permeabilidad de AP-BL. Los resultados indicaron que el transporte intestinal de dihidromiricetina fue un transporte activo dependiente del tiempo y la concentración. La apertura de las uniones celulares tiene poca influencia en la permeabilidad a la dihidromiricetina en ambas direcciones, lo que indica que la vía paracelular no estaba implicada en el transporte de dihidromiricetina. La disminución en el Papp(BL-AP) a 4 °C con respecto al Papp(BL-AP) a 37 °C indica que el flujo de salida de la dihidromiricetina fue un transporte dependiente de la energía. Tanto el verapamil como la ciclosporina A podrían aumentar el Papp(AP-BL) y disminuir el valor de Papp(BL-AP). Sin embargo, MK571 o reserpina no tienen efectos obvios en el transporte de dihidromiricetina. Estos resultados indicaron que la dihidromiricetina podría ser un sustrato de P-gp, aunque no es un sustrato de BCRP y MRP2. La P-gp estaba implicada en el transporte de dihidromiricetina, que dificultaba la absorción de dihidromiricetina en el intestino, y la interacción fármaco-fármaco podía producirse cuando la dihidromiricetina se coadministra con inhibidores de la P-gp.

KEY WORDS: Caco-2 cell, dihydromyricetin, drug-drug interaction, P-gp.

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