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Influence of Grapefruit Juice on the Pharmacokinetics of Curculigoside in Rats

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***SUMMARY*. Curculigoside is a major bioactive phenolic glycoside compound isolated from *Curculigo orchioides* Gaertn. and possesses numerous pharmacological activities. This study investigates the food-drug interaction between grapefruit juice (GFJ) and curculigoside *in vivo* and *in vitro*. The pharmacokinetics of orally administered curculigoside (20 mg/kg) with or without GFJ pretreatment were investigated in rats. Caco-2 cell transwell model and rat liver microsomes incubation systems were also used to support the *in vivo* pharmacokinetic data and investigate its potential mechanism. The results indicated that co-administration of GFJ could increase the systemic exposure of curculigoside significantly, including area under the curve (666.10 ± 124.92 vs. 316.39 ± 88.63 ng·h/mL) and maximum plasma concentration (85.97 ± 9.31 vs. 68.21 ± 6.85 ng/mL). The apparent permeability of curculigoside across the Caco-2 cell transwell model increased significantly with the pretreatment of GFJ (from 2.28 ± 0.31 × 10^{-6} to 2.91 ± 0.44 × 10^{-6} cm/s cm/s), and the metabolic stability of curculigoside was also increased from 25.7 ± 6.8 to 46.1 ± 8.1 min with the pretreatment of GFJ, and the difference was significant ($p < 0.05$). In conclusion, GFJ could increase the systemic exposure of curculigoside in rats when GFJ and curculigoside were co-administered, and it might work mainly through increasing the absorption of curculigoside by inhibiting P-gp, or through slowing down the metabolism of curculigoside in rat liver by inhibiting the activity of CYP3A4.**

RESUMEN. Curculigoside es un glicósido fenólico bioactivo importante aislado de *Curculigo orchioides* Gaertn. que posee numerosas actividades farmacológicas. Este estudio investiga la interacción alimento-fármaco entre el jugo de toronja (GFJ) y curculigoside *in vivo* e *in vitro*. La farmacocinética de curculigoside administrado por vía oral (20 mg / kg) con o sin pretratamiento con GFJ se investigó en ratas. También se usaron los sistemas de incubación de células transgénicas Caco-2 y sistemas de incubación de microsomas hepáticos de rata para respaldar los datos farmacocinéticos *in vivo* e investigar su mecanismo potencial. Los resultados indicaron que la administración concomitante de GFJ podría aumentar la exposición sistémica de curculigoside de manera significativa, incluido el área debajo de la curva (666.10 ± 124.92 vs. 316.39 ± 88.63 ng·h / mL) y la concentración plasmática máxima (85.97 ± 9.31 vs. 68.21 ± 6,85 ng / ml). La permeabilidad aparente de Curculigoside a través del modelo de transwell de células Caco-2 aumentó significativamente con el pretratamiento de GFJ (de 2,28 ± 0,31 × 10^{-6} a 2,91 ± 0,44 × 10^{-6} cm / s cm / s), y la estabilidad metabólica de curculigoside también se incrementó de 25.7 ± 6.8 a 46.1 ± 8.1 min con el pretratamiento de GFJ, y la diferencia fue significativa ($p < 0.05$). En conclusión, GFJ podría aumentar la exposición sistémica de curculigoside en ratas cuando se administró conjuntamente GFJ y curculigoside, y podría funcionar principalmente al aumentar la absorción de curculigosida al inhibir la P-gp, o al desacelerar el metabolismo de curculigosida en hígado de rata. al inhibir la actividad de CYP3A4.

KEY WORDS: CYP3A4, food-drug interaction. P-gp

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