



## Influence of Grapefruit Juice on Pharmacokinetics of Omeprazole in Rats

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**SUMMARY.** This study investigates the food-drug interaction between grapefruit juice (GFJ) and omeprazole. The pharmacokinetics of orally administered omeprazole (2 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 omeprazole significantly, including area under the curve ( $1060.93 \pm 169.82$  vs.  $597.72 \pm 148.06$  ng.h/mL) and maximum plasma concentration ( $333.05 \pm 28.67$  vs.  $226.96 \pm 18.66$  ng/mL). The area under the curve ( $183.91 \pm 22.84$  vs.  $319.28 \pm 16.64$  ng.h/mL) and maximum plasma concentration ( $65.89 \pm 7.28$  vs.  $98.71 \pm 10.85$  ng/mL) of 5-hydroxy-omeprazole (metabolite of omeprazole) decreased significantly with the pretreatment of GFJ. The apparent permeability of omeprazole across the Caco-2 cell transwell model increased significantly with the pretreatment of GFJ (from  $2.28 \pm 0.31 \times 10^{-6}$  to  $2.91 \pm 0.44 \times 10^{-6}$  cm/s), and the metabolic stability of omeprazole was also increased from  $25.7 \pm 6.8$  to  $46.1 \pm 8.1$  min with the pretreatment of GFJ ( $p < 0.05$ ). In conclusion, GFJ could increase the systemic exposure of omeprazole in rats when GFJ and omeprazole was co-administered, and it might work mainly through increasing the absorption of omeprazole by inhibiting *P-gp*, or through slowing down the metabolism of omeprazole in rat liver by inhibiting the activity of CYP3A4.

**RESUMEN.** Este estudio investiga la interacción de alimentos y medicamentos entre el jugo de pomelo (GFJ) y el omeprazol. La farmacocinética de omeprazol administrado por vía oral (2 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 significativamente la exposición sistémica de omeprazol, incluido el área debajo de la curva ( $1060.93 \pm 169.82$  vs.  $597.72 \pm 148.06$  ng.h/mL) y la concentración plasmática máxima ( $333.05 \pm 28.67$  vs.  $226.96 \pm 18.66$  ng/mL). El área bajo la curva ( $183.91 \pm 22.84$  vs.  $319.28 \pm 16.64$  ng.h/mL) y la concentración plasmática máxima ( $65.89 \pm 7.28$  vs.  $98.71 \pm 10.85$  ng/mL) de 5-hidroxi-omeprazol (metabolito de omeprazol) disminuyeron significativamente con el pretratamiento de GFJ. La aparente permeabilidad de omeprazol a través del modelo de transwell de células Caco-2 aumentó significativamente con el pretratamiento de GFJ (de  $2.28 \pm 0.31 \times 10^{-6}$  a  $2.91 \pm 0.44 \times 10^{-6}$  cm/s), y la estabilidad metabólica de omeprazol también aumentó de  $25.7 \pm 6.8$  a  $46.1 \pm 8.1$  min con el pretratamiento de GFJ ( $p < 0.05$ ). En conclusión, GFJ podría aumentar la exposición sistémica de omeprazol en ratas cuando se administraron concomitantemente GFJ y omeprazol, y podría funcionar principalmente al aumentar la absorción de omeprazol al inhibir la *P-gp*, o al desacelerar el metabolismo del omeprazol en el hígado de rata al inhibir la actividad de CYP3A4.

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

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