Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense)*
Lat. Am. J. Pharm. **37** (8): 1558-63 (2018)

Received: May 23, 2018
Revised version: June 5, 2018
Accepted: June 6, 2018

Effects of Verapamil on the Pharmacokinetics of Asiatic Acid in Rats and its Potential Mechanism

Lu LIU [1 #], Xiaoliang LI [2 #], Yong LIANG [3 #] & Xiaohua LI [1 *]

[1] *Department of Endocrinology, Seventh People's Hospital of Shanghai University of TCM, Shanghai 200137, China*

[2] *Department of Pharmacy, Yidu Central Hospital of Weifang, Shandong 262500, China*

3 Department of Urology Surgery, Caoxian people's Hospital, Heze 274400, Shandong province, China

***SUMMARY*. The low oral bioavailability of asiatic acid hinders its pharmacological effects and clinical application. This study investigates the effects of verapamil on the pharmacokinetics of asiatic acid in rats and clarifies the main mechanism underlying its poor oral bioavailability. The pharmacokinetics of asiatic acid (20 mg/kg) in rats with or without pretreatment with verapamil (10 mg/kg) were determined. Then, the effects of verapamil on the transportation and metabolism of asiatic acid were investigated using a Caco-2 cell transwell model and rat liver microsome incubation systems. The results indicated that verapamil could significantly increase the C_{max} (from 328.52 to 406.35 ng/mL), and $t_{1/2}$ (from 1.25 ± 0.15 to 1.56 ± 0.21 h) of asiatic acid ($P < 0.05$). Verapamil could significantly increase the absorption of asiatic acid in the Caco-2 cell monolayer model. Additionally, the intrinsic clearance rate of asiatic acid decreased significantly (from 123.20 to 74.16 μL/min/mg protein) ($P < 0.05$) with verapamil pretreatment. These results indicated that verapamil could increase the systemic exposure of asiatic acid in rats, and the poor absorption due to P-Glycoprotein *(P-gp)* mediated efflux in the intestine and the high intrinsic clearance rate in the rat liver mediated by CYP3A4 may be the main reasons for the poor oral bioavailability of asiatic acid.**

RESUMEN. La baja biodisponibilidad oral del ácido asiático dificulta sus efectos farmacológicos y su aplicación clínica. Este estudio investiga los efectos del verapamilo en la farmacocinética del ácido asiático en ratas y aclara el mecanismo principal que subyace a su escasa biodisponibilidad oral. Se determinó la farmacocinética del ácido asiático (20 mg/kg) en ratas con o sin pretratamiento con verapamilo (10 mg/kg). Luego se investigaron los efectos del verapamilo sobre el transporte y el metabolismo del ácido asiático utilizando un modelo de transwell de células Caco-2 y sistemas de incubación con microsomas de hígado de rata. Los resultados indicaron que el verapamilo podría aumentar significativamente la C_{max} (de 328,52 a 406,35 ng/ml) y el $t_{1/2}$ (de 1.25 ± 0.15 a 1.56 ± 0.21 h) de ácido asiático ($P < 0.05$). El verapamilo podría umentar significativamente la absorción de ácido asiático en el modelo de monocapas de células Caco-2. Además, la tasa de aclaramiento intrínseco del ácido asiático disminuyó significativamente (de 123.20 a 74.16 μL/min/mg de proteína) ($P < 0.05$) con el pretratamiento con verapamilo. Estos resultados indican que el verapamilo podría aumentar la exposición sistémica del ácido asiático en ratas, y la escasa absorción debida al eflujo mediado por la P-Glicoproteína *(P-gp)* en el intestino y la alta tasa de aclaramiento intrínseco en el hígado de rata mediado por CYP3A4 serían las principales razones de la pobre biodisponibilidad oral del ácido asiático.

KEY WORDS: asiatic acid, CYP450, oral bioavailability, P-Glycoprotein, verapamil.

# The first three authors contributed equally to this work.
* Author to whom correspondence should be addressed. *E-mail:* xiaohua_li16@163.com

ISSN 0326 2383 (printed ed.)
ISSN 2362-3853 (on line ed.)