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20(S)-Protopanaxatriol Alters the Toxicity Response of Irinotecan Through Affecting the Pharmacokinetics of Irinotecan

Yimin FU [1] #, Meihua REN [2] #, Shengpin ZHAI [3] *& Tingshu JIANG [3] *

[1] *Health Department, Yantai Yuhuangding Hospital affiliated to Qingdao University, Yuhuangding East Road No. 20, Zhifu District, Yantai City, Shandong Province, China.*

[2] *Cardiology Department, Yantai Harbor Hospital, Xingfu Road No. 100, Zhifu District, Yantai City, Shandong Province, China.*

[3] *Respiratory Department, Yantai Yuhuangding Hospital affiliated to Qingdao University, Yuhuangding East Road No. 20, Zhifu District, Yantai City, Shandong Province, China*

SUMMARY. **The influence of 20(S)-protopanaxatriol (PPT) towards the intestinal toxicity of irinotecan was evaluated in the present study. Seven days oral gavage of 300 mg/kg of PPT significantly increased irinotecan (i.p., 50 mg/kg, 5 day)-induced intestinal toxicity, as demonstrated by the elevated damage of ileum. Detailed reason was elucidated through evaluating the inhibition of PPT towards the glucuronidation activity of SN-38, which is the active metabolite of irinotecan. The results showed that 0.05, 0.1, 0.25, 0.5, 1, 2.5, 5, and 10 uM of PPT inhibited recombinant UGT1A1-catalyzed glucuronidation of SN-38 by -18.8, 22.1, 41.1, 65.2, 71.9, 85.4, 90.5, and 92.3%, respectively. The activity of human liver microsomes (HLMs)-catalyzed SN-38 glucuronidation was inhibited by 36.5, 46.8, 52.7, 60.9, 73.4, 79.9, 83.9, and 88.7% at 0.1, 0.25, 0.5, 1, 2.5, 5, 10, and 25 uM of PPT. PPT competitively inhibited recombinant UGT1A1 and HLMs-catalyzed SN-38 glucuronidation. All these results indicated that PPT can increase the toxicity of irinotecan through inhibiting the glucuronidation reaction of its active metabolite SN-38.**

RESUMEN. En el presente estudio se evaluó la influencia del 20(S)-protopanaxatriol (PPT) en relación a la toxicidad intestinal de irinotecán. Luego de 7 días de ingesta por sonda oral de 300 mg/kg de PPT aumentó significativamente la toxicidad intestinal inducida por irinotecan (i.p., 50 mg/kg, 5 días), como se demuestra por el daño elevado del íleon. El mecanismo fue aclarado a través de la evaluación de la inhibición de la actividad de PPT hacia la glucuronidación de SN-38, que es el metabolito activo del irinotecan. Los resultados mostraron que 0,05, 0,1, 0,25, 0,5, 1, 2,5, 5 y 10 uM de PPT inhiben la glucuronidación de SN-38 catalizada por UGT1A1 recombinante en -18.8, 22.1, 41.1, 65.2, 71.9, 85.4, 90.5 y 92.3%, respectivamente. La actividad de microsomas de hígado humano (HLMs) catalizada por la glucuronidación de SN-38 se inhibió en un 36,5, 46,8, 52,7, 60,9, 73,4, 79,9, 83,9 y 88,7% frente a PPT 0,1, 0,25, 0,5, 1, 2,5, 5, 10 y 25 μM. PPT inhibe competitivamente la glucuronidación de UGT1A1 recombinante y de HLMs catalizada por SN-38. Todos estos resultados indican que PPT puede aumentar la toxicidad del irinotecán a través de la inhibición de la reacción de glucuronidación de su metabolito activo SN-38.

KEY WORDS: Irinotecan, 20(S)-protopanaxatriol (PPT), Toxicity.

* Authors to whom correspondence should be addressed. *E-mails:* fengqiaoyebo@163.com (Shengpin Zhai), oy56997@126.com (Tingshu Jiang).

\# These two authors equally contributed to this work.

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