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Effect of Crocetin on Cytochrome P450 Isoforms *In Vitro*

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***SUMMARY*. The activity of CYP450s was evaluated in pooled human liver microsomes (HLMs) in the presence of crocetin with various concentrations. The inhibition characteristics were estimated by fitting with the Lineweaver-Burk plots. Crocetin was found to significantly inhibit the activity of CYP3A4, 2C9, and 2E1 in a dose-dependent manner with the IC_{50} values of 18.04, 12.71, and 8.53 μM, respectively. The non-competitive manner was observed in the inhibition of CYP3A4 with the K_i value of 9.89 μM, while the inhibition of CYP2C9 and 2E1 was performed competitively with K_i values of 6.13 and 4.22 μM, respectively. Interestingly, a time-dependent manner was found during the inhibitory effect of crocetin on CYP3A4 activity. The K_I value was 3.20 μM^{-1} and the K_{inact} value was 0.040 min^{-1}. The obtained results demonstrated the inhibitory effect of crocetin on the activity of CYP3A4, 2C9, and 2E1, which implies the potential of crocetin to interact with co-administrated drugs and provides guidance for its clinical application.**

RESUMEN. La actividad de CYP450 se evaluó en microsomas de hígado humano (HLM) agrupados en presencia de crocetina con diversas concentraciones. Las características de inhibición se estimaron ajustando las gráficas de Lineweaver-Burk. Se encontró que la crocetina inhibe significativamente la actividad de CYP3A4, 2C9 y 2E1 de una manera dependiente de la dosis con los valores de CI50 de 18.04, 12.71 y 8.53 μM, respectivamente. La forma no competitiva se observó en la inhibición de CYP3A4 con el valor de Ki de 9,89 μM, mientras que la inhibición de CYP2C9 y 2E1 se realizó de forma competitiva con valores de Ki de 6,13 y 4,22 μM, respectivamente. Curiosamente, se encontró una manera dependiente del tiempo durante el efecto inhibidor de la crocetina sobre la actividad de CYP3A4. El valor de KI fue de 3,20 μM^{-1} y el valor de Kinact fue de 0,040 min^{-1}. Los resultados obtenidos demostraron el efecto inhibidor de la crocetina sobre la actividad de CYP3A4, 2C9 y 2E1, lo que implica el potencial de la crocetina para interactuar con fármacos coadministrados y proporciona una guía para su aplicación clínica.

KEY WORDS: competitive inhibition, crocetin, CYP450 enzymes, drug-drug interaction, non-competitive inhibition

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