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A major constituent from Zanthoxylum nitidum, compound X, is a naturally occurring antagonist of the human and rat pregnane X receptor

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Discrepancy expression and regulation of drug-metabolizing enzymes (DMEs) is a common cause of adverse drug effects in some drugs with narrow therapeutic index (TI). A important cytochrome P450 3A4 (CYP3A4) is predominantly regulated by a nuclear receptor, pregnane X receptor (PXR). A pure compound isolated from *Zanthoxylum nitidum*, compound X, exhibits variety of biological functions, however the effect of compound X on the modulation of CYP3A4 is not well understood. In this study, the effects of compound X on the PXR-CYP3A4 pathway, and the underlying mechanisms, were characterized. Compound X potently and dose-dependently attenuated CYP3A4 induction by blocking the activation of nuclear receptors, especially PXR. Further mechanistic studies revealed that compound X inhibited PXR by interrupting the binding of steroid receptor cofactor-1 (SRC-1) and hepatocyte nuclear factor 4α (HNF4α). Our results may lead to the development of important new therapeutic and dietary approaches to reduce the frequency of undesirable drug interactions. Here, we established compound X as a novel and natural potent inhibitor of PXR and can be a useful tools for modulating DME expression and drug efficacies. Modification of CYP3A4 expression and activity by

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