In Vitro Inhibitory Effects of Herbal Supplements on Tamoxifen and Irinotecan Metabolism
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Purpose
Determine inhibitory effects of ten commonly used over-the-counter herbal supplements on the in vitro enzymatic bioactivation of two chemotherapeutic prodrugs: tamoxifen and irinotecan.

Methods
Tamoxifen or Irinotecan were incubated with various concentrations of ten herbal supplements. Reactions were carried out at 37°C with a NADPH regenerating system and pooled human liver microsomes in triplicate. Reactions were quenched with an equal volume of acetonitrile containing terfenadine as an internal standard. Samples were centrifuged and the supernatant analyzed by LC-MS/MS. Separation was achieved using a Luna C18 column (100 x 2.1 mm) with a gradient elution using an AB Sciex 4000 QTRAP mass spectrometer.

Results
Of the ten herbal supplements tested, four (echinacea, ginseng, skullcap and lemon balm) were found to inhibit the CYP450 mediated bioactivation of tamoxifen to its active metabolites, while only two (skullcap and lemon balm) inhibited the carboxyesterase bioactivation of irinotecan. The inhibition was characterized by determining the IC50 values of each herbal inhibitor on the formation of each active metabolite(s). For the 4-hydroxytamoxifen metabolite the measured IC50 values for echinacea, ginseng, skullcap and lemon balm were 2.2 ± 0.06, 6.7 ± 0.2, 2.01 ± 0.4, 1.2 ± 0.03 mg/mL, respectively. For endoxifen the measured IC50 values for echinacea, ginseng, skullcap and lemon balm were 1.07 ± 0.04, 3.6 ± 0.2, 1.01 ± 0.04, 0.38 ± 0.02, respectively. While the desmethyltamoxifen isn’t an active metabolite its IC50 values for each herbal was measured since it is a precursor metabolite to endoxifen. For desmethyltamoxifen the IC50 values for echinacea, ginseng, skullcap and lemon balm were 1.75 ± 0.04, 4.8 ± 0.1, 1.35 ± 0.02, 0.65 ± 0.03 mg/mL, respectively. IC50 values for inhibition of the irinotecan activation to its active metabolite SN-38 by skullcap and lemon balm were 4.1 ± 0.6, 5.1 ± 0.3 mg/mL, respectively.

Conclusion
Based on our in vitro measured IC50 values the use skullcap and lemon balm with tamoxifen would have the greatest potential for a sub-therapeutic clinical exposure of the active metabolites. It is unlikely these herbals would have a negative effect on the efficacy of irinotecan. Clinical evaluations are needed to confirm the in vitro results.