P.O. Box 144345 Austin, TX 78714-4345 ▪ 512.926.4900 ▪ Fax: 512.926.2345 ▪ www.herbalgram.org

HerbClip™

File: ■ Milk Thistle (*Silybum marianum*)
■ Herb-drug Interactions
■ CYP Enzymes

HC 111354-493

Date: March 31, 2014

RE: Effect of Milk Thistle Extracts and Isolated Constituents on CYP3A Enzyme Activity

Brantley SJ, Graf TN, Oberlies NH, Paine MF. A systematic approach to evaluate herb-drug interaction mechanisms: Investigation of milk thistle extracts and eight isolated constituents as CYP3A inhibitors. *Drug Metab Dispos*. 2013;41(9):1662-1670.

Herb-drug interactions are not routinely evaluated; however, they can have meaningful consequences. For example, if an herb inhibits liver cytochrome P450 activity, then systemic concentrations of a drug taken concomitantly may increase and potentially lead to adverse effects and toxicity. Most commercial milk thistle (*Silybum marianum*) products contain the extract fraction silymarin (which contains at least seven flavonolignans, the flavonoid taxifolin, and fatty acids) or less frequently silibinin, and a more highly purified extract that consists of the most prevalent flavonolignans (silybin A and silybin B). In vitro studies have found that milk thistle extracts inhibit several cytochrome P450 enzymes; however, clinical studies do not always support the in vitro findings (possibly due to variations in the composition of products or bioavailability). Cytochrome CYP3A metabolizes >30% of all drugs in the intestines and liver which could be potentially inhibited by oral milk thistle extract. The objectives of this in vitro study were to assess the potential interaction of silymarin, silibinin, and other individual constituents of milk thistle toward CYP3A activity, to prioritize constituents for further evaluation, and to develop a framework to elucidate mechanisms underlying herb-drug interactions.

Human liver microsomes (HLMs) and human intestinal microsomes (HIMs) were incubated with midazolam (a commonly used drug that is metabolized by CYP3A), silymarin, and constituents of milk thistle (silybin A, silybin B, isosilybin A, isosilybin B, silychristin, isosilychristin, silydianin, and taxifolin) to evaluate their inhibitory effect on midazolam metabolism. Silymarin (16% silybin A, 24% silybin B, 6.4% isosilybin A, 4.4% isosilybin B, 17% silydianin, 12% silychristin, 2.2% isosilychristin, and 1.6% taxifolin; the remainder consists of uncharacterized polyphenols and aliphatic fatty acids) was obtained from Euromed S.A.; Barcelona, Spain. The isolated constituents were purified to >90% as determined by high-performance liquid chromatography (HPLC).

All of the isolated flavonolignans, silibinin, and silymarin inhibited midazolam metabolism in a concentration-dependent manner in HLMs and HIMs, except isosilychristin in HIMs. Taxifolin produced no concentration-dependent inhibition. Only silybin B (HLMs) and silychristin and silydianin (HIMs) showed concentration-dependent inhibition from 1 to 10 μM. At 100 μM concentration, silybin A was the most potent inhibitor in HLMs (>50% inhibition of CYP3A activity), followed by silymarin, isosilybin B, and isosilybin A. At 100 μM, silymarin was the most potent in HIMs (>50% inhibition of CYP3A activity), followed by isosilybin A, isosilybin B, and silychristin. The IC_{50s} for isosilybin B and silychristin in HIMs were ~60 and 90 μM, respectively, whereas those for the remaining constituents were >100 μM. Extracts and constituents that contained the 1,4-dioxane moiety demonstrated a >1.5-fold shift in IC_{50} when tested as potential mechanism-based inhibitors. The semipurified extract, silibinin, and the two associated constituents (silybin A and silybin B) demonstrated mechanism-based inhibition (MBI) of recombinant CYP3A4 but not microsomal CYP3A activity. The maximum predicted increases in midazolam area under the curve using the static mechanistic equation using recombinant CYP3A4 were 1.75-fold, which may necessitate clinical assessment.

In summary, all milk thistle constituents differentially inhibited CYP3A-mediated midazolam 19-hydroxylation metabolism. Silymarin was consistently one of the most potent inhibitors of CYP3A activity in microsomal preparations. Of the 8 isolated constituents, the relatively less abundant isosilybin A and isosilybin B were two of the more potent inhibitors in both HLMs and HIMs. The low systemic exposure of silybin A and silybin B following milk thistle administration indicate a low risk for an interaction between CYP3A and milk thistle at typical doses. Products enriched with these constituents, such as silibinin, may have increased herb-drug interaction liability compared with other milk thistle products. The authors suggest that the risk of milk thistle-drug interactions may be limited to drugs sensitive to extensive intestinal first-pass metabolism (e.g., simvastatin and felodipine) and/or to patient populations at risk for elevated milk thistle exposure (e.g., impaired hepatic function). Further evaluation is needed to assess this possibility and confirm the potential for synergistic inhibition of CYP3A by milk thistle flavonolignans.

—Heather S. Oliff, PhD

The American Botanical Council has chosen not to include the original article.