

Milk Thistle and the Liver: Recent Findings

by Kerry Bone

Milk thistle (*Silybum marianum*) is a native to the Mediterranean region but has been introduced to most areas of the world where it is often regarded as a weed. Its use as a liver herb appears to have originated from Germany¹ and more recently a concentrated, standardized extract has been extensively investigated as an antioxidant and hepatoprotective agent.

The standardized extract contains flavonolignans, collectively referred to as silymarin. Sometimes the extract itself is called "silymarin", which can lead to confusion over dosage since the level of flavonolignans (silymarin) in the extract is typically 60 to 80%, depending on the test methodology used. The main flavonolignans found in the extract are silybin (silibin), silychristin, silydianin and 2,3 dehydro derivatives. Silybin is the predominant flavonolignan and many pharmacological studies have been on this compound alone.

In this month's column some of the key published articles on standardized milk thistle extract published in the last few years have been reviewed along relevant themes.

Hepatitis C

One important question posed by a recent publication was: "Does *Silybum marianum* play a role in the treatment of chronic hepatitis C?"² In this study, which was an open label controlled trial involving 34 patients, milk thistle extract at 480 mg per day for 4 weeks was compared to no treatment in patients with chronic hepatitis C not using antiviral therapy. Blood tests for viral load and liver enzymes (ALT and AST) were done at randomization and at the end of treatment. The paired-t test was used to measure differences between baseline and week 4 values for ALT, AST and viral load. Mean baseline measurements of AST, ALT and viral load in the treatment group were 85 ± 12.41 IU/mL, 120 ± 20.57 IU/mL and 8.77 ± 4.12 copies x $10(6)$ /mL, while for the no-treatment group they were 71 ± 9.46 IU/mL, 97 ± 15.35 IU/mL and 1.8 ± 0.62 copies x $10(6)$ /mL respectively. For treated subjects the mean values of AST, ALT and viral load demonstrated a decrease from baseline values, but this difference was not statistically significant. For control patients the values of ALT ($p=0.049$), AST ($p=0.005$) and viral load ($p=0.005$)

showed a statistically significant increase at week 4. The percent change for ALT ($p=0.014$), AST ($p=0.002$) and viral load ($p=0.326$) compared between the treated and control group demonstrated a statistically significance difference for ALT and AST, but not for viral load. No side effects were reported using the herb extract.

The authors concluded that milk thistle is a well tolerated treatment associated with a decrease in measures of liver damage but with no apparent effect on viral load. They suggested it might have a protective effect in the inflammatory response to the hepatitis C virus, but no role as an antiviral agent.

Commentary

These results are as expected since milk thistle has never been claimed to have significant antiviral activity. However, even the hepatoprotective role of milk thistle has been questioned in some studies involving hepatitis C patients. For example a small pilot study in 24 patients over 12 weeks found no improvement in ALT or viral loads from either 600 or 1200 mg/day of milk thistle extract.³ Two other studies found similar negative results.^{4,5}

The findings from these more recent trials contrast with those of earlier trials. For example a systematic review examined studies published up to the year 2000 on the use of milk thistle extract in patients with chronic liver disease, including hepatitis C.⁶ Milk thistle treatment resulted in a statistically significant decrease in transaminases (liver enzymes) in 4 studies compared to baseline and in one study compared to placebo. Although a reduction in transaminase levels has uncertain clinical significance, the authors of the review pointed out that such are purely biochemical (as opposed to viral) response may be beneficial in the long term.

Based on these findings it can be concluded that milk thistle should not be solely relied on for the treatment of hepatitis C, but may have some role as an hepatoprotective agent.

Potential Herb-Drug Interactions

A common misconception concerning milk thistle is that, since it is a liver herb, it is likely to increase the metabolism and clearance of many drugs due to enhanced hepatic detoxification. This is certainly fuelled by *in vitro* studies showing this effect and an *in vivo* study in rats where high doses increased phase I hepatic metabolism.⁷ Oral administration of milk thistle extract (100 mg/kg/day) to rats resulted in a significant increase in the activity of the mixed-function oxidation system (cytochrome P450; aminopyrine demethylation, p-nitroanisole demethylation). However, an experimentally-induced reduction in activities of the mixed-function oxidation system and glucose-6-phosphatase could not be prevented by pretreatment with milk thistle.⁷

In human volunteers, treatment with milk thistle extract (210 mg/day for 28 days) had no influence on the metabolism of aminopyrine or phenylbutazone.⁸ Concentrated milk thistle extract at commonly administered doses did not interfere with indinavir therapy in patients with HIV.⁹

This lack of interaction with indinavir was verified in a later randomized, controlled pharmacokinetic study.¹⁰ The publication also included a meta-analysis of 3 clinical trials which found that consumption of milk thistle extract did not alter indinavir levels in the blood.

In other words, despite the findings of *in vitro* and *in vivo* studies, there was no evidence from clinical studies that milk thistle extract increases phase I/II liver metabolism. The reason behind this discrepancy is probably that normal clinical doses are not high enough to achieve the effects shown at the artificially high doses used in experimental models.

One investigation that appears to challenge this position was a clinical study in 12 healthy volunteers.¹¹ At first, subjects received metronidazole (Flagyl; a substrate for cytochrome CYP3A4 and CYP2C9) alone at a dose of 400 mg every 8 h for 3 days. On day 4, blood and urine were collected at different time points and metronidazole levels were measured. After a washout period of one week, milk thistle extract was given at a daily dose of 140 mg for 9 days. From day 7 both milk thistle extract (140 mg/day) and metronidazole (3 x 400 mg/day) were given till the 9th day. On day 10 blood and urine were collected as above and the levels of metronidazole and its metabolite were measured. Administration of milk thistle increased the clearance of metronidazole and its major metabolite, hydroxy-metronidazole (HM) by 29.51% and 31.90% respectively, with a concomitant decrease in half-life and maximum concentration. Urinary excretions of acid-metronidazole, HM and metronidazole were all decreased.

The key to understanding this particular study is the decreased levels of metronidazole and its metabolites in serum and urine. This suggests reduced absorption into the bloodstream via the induction of the drug transporting P-glycoprotein (P-gp), particularly at the level of the intestine. P-gp is a molecule that acts as a drug efflux pump at epithelial cells, especially the intestinal wall. In other words, induction of P-gp results in less absorption of any drug that is subject to its effects. So the most likely explanation of the findings is a reduced uptake due to P-gp induction, rather than increased clearance resulting from the induction of hepatic phase I cytochrome P450 enzymes such as CYP3A4. Nonetheless, it suggests the possibility that milk thistle could reduce the oral bioavailability of other drugs susceptible to P-gp, which include paclitaxel and digoxin.

This potential pharmacokinetic interaction of milk thistle with digoxin was recently put to the test in a clinical study involving 16 healthy volunteers.¹² Milk thistle extract was given at the high dose of 900 mg per day for 14 days. A statistically significant impact of milk thistle on digoxin pharmacokinetics was not observed, although there was a trend that approached significance. The authors concluded that milk thistle and black cohosh (which was also part of the study) do not appear to substantially affect digoxin pharmacokinetics, suggesting that they are not potent modulators of P-gp *in vivo*.

Finally, the impact of milk thistle on the pharmacokinetics of the anticancer drug irinotecan was investigated in 6 cancer patients.¹³ This was an important study because milk thistle can be useful to minimize some of the toxic effects of chemotherapy, but concerns have been expressed over possible interactions. Patients receiving irinotecan by intravenous infusion once a week were also administered 600 mg milk thistle extract for 14 days. The timing of the chemotherapy drug treatments meant that doses of irinotecan were administered to patients at 4 and 12 days after taking the milk thistle. Irinotecan pharmacokinetics were found not to be impacted by the milk thistle to a clinically significant extent at either time point.

Commentary

I have often heard colleagues express reservations about recommending milk thistle extract during chemotherapy or for patients undergoing general anesthesia. These concerns are largely based on potential herb-drug interactions, although an antioxidant effect may also be of concern during chemotherapy. Certainly from the perspective of interactions such reservations have no basis.

In the case of general anesthesia I have found relatively high doses of milk thistle extract for 3 weeks prior and 4 to 8 weeks after general anesthesia to be greatly beneficial in minimizing its toxic effect. The longer the patient is

under surgery, the longer milk thistle is given after the event. For example, for 1 to 2 hours of surgery it is recommended for 4 weeks after, for 6 hours 6 weeks after and so on. No adverse effects have been observed from this protocol and most patients report considerable benefit.

There is evidence to support such a practice. Milk thistle administered during the pre- and post-operative period prevented the increase of hepatic enzymes in the serum induced by the toxic effect of general anesthesia.¹⁴ Milk thistle also improved liver function in patients who had been exposed for many years to halogenated hydrocarbons.¹⁵ Treatment with milk thistle extract (420 mg per day) in patients with occupational toxic hepatopathy caused by various toxic substances (mostly solvents, paints and glues) resulted in slight variations in some parameters compared to those treated with placebo. The therapeutic effect of milk thistle was more evident when the exposure period to toxins was shorter.¹⁶

Type 2 Diabetes

While type 2 diabetes is not a disease of the liver, this organ is involved in blood sugar regulation. Moreover, the development of non-alcoholic fatty liver disease is often associated with metabolic syndrome, a precursor state to type 2 diabetes.¹⁷ So it is interesting to note that milk thistle extract was found to be useful in type 2 diabetes in a recent clinical trial, with associated improvements in liver function (damage) tests.¹⁸ In this randomized, double blind, controlled trial, 51 type 2 diabetic patients received either 600 mg/day of milk thistle extract as a divided dose before meals or a matching placebo for 4 months. The milk thistle extract was in addition to the oral hypoglycemic drugs metformin and glibenclamide. At the end of 4 months fasting blood sugar was significantly decreased in the milk thistle group (156±46 mg/dL at baseline down to 133±39 mg/dL, p=0.001) and significantly increased for placebo (167±47 mg/dL up to 188±48 mg/dL, p=0.001). Glycosylated hemoglobin also showed the same significant trends: 7.8±2.0% down to 6.8±1.1% for milk thistle (p=0.001) versus an increase from 8.3±1.9% to 9.5±2.2% for placebo (p=0.0001). Compared to baseline, total cholesterol, LDL cholesterol and triglycerides were all significantly reduced by the milk thistle treatment by 12%, 12% and 26%, respectively. There were no significant changes in these parameters for the placebo group. As might be expected, the milk thistle significantly decreased even the normal levels of transaminases (ALT and AST) found, with no change in these parameters for the placebo group.

Commentary

This clinical trial suggests that milk thistle can be an extremely useful adjunct to conventional drug therapy for type 2 diabetes which can lead to improved glycemic control, reduced transaminases and a better blood lipid

profile. It is very likely that these effects are mediated by an influence on liver function from this well-known hepatic herb.

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