Milk Thistle (*Silybum marianum*)

Milk thistle is a well known and commonly used herb, used particularly in hepatic diseases. It has very potent antioxidant, anti-inflammatory, and antifibrotic properties (1). As a single agent its therapeutic effects in liver disease appear to be modest (2,3,4,5). Herbal medicines and supplements are likely to be much more beneficial when used synergistically in combinations or formulas. Milk thistle preparations have also shown promise *in vitro* in the treatment of malignancies. They have been shown to have beneficial cell cycle and antiangiogenic properties (6,7), and inhibition of telomerase activity (8). They have been tested in various tumor types with promising effects (7,8).

The use of any herb in oncology needs to be considered regarding potential drug-herb interactions. This is even more so in the case of an herb which is know to affect liver function. Various drug detoxifying functions occur primarily in the liver, such as the cytochrome p450 and phase 2 deconjugation reactions. In fact, milk thistle preparations have primarily been employed in conventional practice in cases of potential drug toxicity, such as with poisonous mushrooms and CCL4 with significant protection against hepatic failure.

Some studies have shown synergistic effects when milk thistle preparations have been studied in combination with chemotherapeutic agents. Singh studied silibinin (one of the main active components in milk thistle) in combination with doxorubicin and found enhanced activity in an athymic mice with lung tumors. Indexes of cell proliferation, angiogenesis and apoptosis showed benefit. Silbinin was shown to inhibit NFkB and COX -2, which are known to promote drug resistance (9). Bokemeyer studied silibinin in combination with cisplatinum and amifostine in a rat germ tumor cell model, and found protection against nephrotoxicity and ototoxicity, as well as no evidence of a negative effect on the cytotoxicity of these agents. He suggested further study in patients with testicular cancer (10). No effect was found when a milk thistle preparation was administered with indinavir, an antiviral agent (11). Tyagi found synergism with doxorubicin, cisplatinum and carboplatinum in a breast cancer cell line (12). Specific studies on effects on the p450 and phase 2 deconjugation reactions have been mixed (13,14,15). Zhou noted a beneficial effect on P-Glycoprotein which is involved in multidrug resistance gene pathways, where milk thistle acted opposite to St. Johns Wort, an herb which has been shown to have worrisome drug-herb interactions (16).

As has been discussed in the section on antioxidants and malignancies, significant concern exists regarding potential negative interactions between antioxidants and chemotherapy and radiation therapy. There are rationale theoretical reasons behind this concern, though there is little in the way of evidence based medicine to support it. However, a different situation exists regarding the interaction of anti-inflammatory interventions used in conjunction with chemotherapy and radiation therapy. Various physiological processes, often involving NFkB and COX-2 enzymes, are upregulated when chemotherapy and radiotherapy are administered. The upregulation has the effect of decreasing the

effectiveness of these interventions. Herbs containing concentrated amounts of flavonoids have multiple effects, including being potent antioxidants and anti-inflammatory agents. The vast majority of the literature on these substances, which is confirmed in those studies cited above, suggests that these herbs enhance efficacy of chemotherapy and radiation therapy, as well as potentially decreasing adverse treatment reactions. If this occurs primarily through their anti-inflammatory effects isn't known.

Reducing free radicals through antioxidants also has an anti-inflammatory result, and it's physiologically entirely conceivable to expect that the antioxidant and antiiflammatory actions support each other. This might not be the case with the antioxidant vitamins beta-carotene and tocopherols when used in conjunction with chemotherapy and radiation therapy.

A range of milk thistle preparations exist, standardized to concentrations of different components, including silibinin and silymarin. In addition, a product which is pharmaceutically combined with phosphatidyl choline (known as IdB 1016 and available in the U.S. as silybin phytosome through the company Phytopharmica) appears to be particularly promising with regards to concentrations and potency (17). This is of great importance, as there are significant concerns regarding the bioavailabily of flavonoid compounds. Therapeutic dosage is likely in the range of 300-500 mg of silibinin daily.

In summary:

- Milk thistle preparations have actions which can be of benefit in patients with different malignancies.
- Thistle flavonoids have both anti-oxidant and anti-inflammatory properties which may act synergistically in combination with certain chemotherapeutic agents, while at the same time providing hepatoprotective effects.
- Issues of dosage are important, and products which are combined with phosphatidyl choline, and are high in silibinin are particularly promising.

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