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Milk thistle: early seeds of potential

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Milk thistle (*Silybum marianum*) has been used for centuries as a medicinal plant; according to folk tradition, its characteristic violet flowers and white-veined leaves came from the Virgin Mary's milk. It is native to the Mediterranean and a member of Asteraceae family, which also includes sunfl owers and daisies. The Greek physician and botanist Dioscorides (40–90 AD) was the first to describe milk thistle's healing properties. Later, in 1597, John Gerard noted that milk thistle was “the best remedy against melancholy diseases”. More recently, a small randomised study from Iran showed similar improvements in patients with obsessive-compulsive disorder who received either fluoxetine or extract derived from leaves of the milk-thistle plant.

The active component of milk thistle is silibin, also known as silybinin, which is usually derived from the seeds of the plant. Silymarin is a complex of biological compounds (flavolignans) that includes silibin; these compounds are known to be antioxidants, in addition to having several other biological properties. Silymarin is registered in the US Chemical Abstracts Service registry, and surveys have found milk thistle to be the most commonly used liver protectant or hepatoprotectant used by patients in gastrointestinal clinics in the USA. In Germany, where the government regulates herbal medicine use, milk thistle has been listed in the Commission E monograph for the treatment of dyspepsia, cirrhosis, and liver damage due to toxins.

Milk thistle's use can range from the mundane—eg, fighting hangovers—to potentially life-saving for patients who have ingested poisonous mushrooms—particularly amanita (deathcap) mushrooms, which release a specific toxic called amatoxin. A review of more than 2000 patients exposed to amanita mushrooms in Europe and North America suggested that intravenous silybinin was the most effective therapy available against this toxin. A trial is in progress in the USA (NCT00915681) examining an intravenous formulation in patients with amatoxin poisoning.

Several smaller studies have also suggested that milk-thistle compounds might have antiviral and anti-inflammatory effects. In particular, milk thistle might eff ectively treat hepatitis C, particularly when given intravenously. However, a larger study of 154 patients with chronic hepatitis C showed that although silybinin was reported to be safe, it had no significant effects on liver enzymes in patients compared with placebo. This study was criticised for giving the medication orally, with lower concentrations observed than when intravenous formulations had been used previously. Mechanisms of antiviral activity against hepatitis C

include inhibition of a viral polymerase critical for replication. Interestingly, a case report of a patient co-infected with both hepatitis C and HIV showed clearance of both hepatitis C and HIV after 2 weeks of intravenous silybinin.

Other attempts at harnessing the hepatoprotective effects of milk thistle have been in patients undergoing chemotherapy, which can often be toxic to the liver. One randomised study of milk thistle in children undergoing aggressive chemotherapy for acute leukaemia suggested that giving milk thistle improved liver function in some of the children, and although there was a trend towards greater chemotherapy doses in those who received milk thistle, this result was not statistically significant. Similarly, there are several case reports in the scientific literature of patients undergoing chemotherapy who had raised concentrations of liver enzymes during treatment for leukaemias that were perhaps improved by administration of milk thistle.

Another dose-finding trial was done in patients with liver cancer who had substantial underlying liver disease. Because chemotherapy can only be administered to patients with relatively preserved liver function, this trial sought to improve underlying liver dysfunction (either from the tumour or severe underlying liver disease) that prevented patients from obtaining standard therapy. Because of shorter-than-expected survival, only three patients were enrolled before stopping the trial. One patient did have a transient improvement in liver enzymes and markers of inflammation after about 2 months in the study, suggesting that testing the drug in a somewhat healthier population of patients (or possibly using a stronger intravenous formulation) might yield more benefits.

Milk-thistle compounds have also shown direct anticancer activities in preclinical models, including inducing apoptosis of colon cancer cells, causing cancer cell senescence in a mouse model of breast cancer, and blocking angiogenesis in prostate cancer models. Milk-thistle compounds painted on the skin of mice exposed to ultraviolet radiation also prevented the development of skin cancers. Notably, the protective effects of milk thistle were seen when it was given either before or after ultraviolet B exposure, suggesting that milk thistle did not simply act as a sunscreen, but rather reduced cancer formation by blocking intrinsic cancer pathways, although the nature of these pathways requires elucidation.

Anticancer activity has not yet been clearly shown in trials in humans. A dose-finding prostate cancer study recommended that 13 g per day of an oral milk-thistle compound (silybin-phytosome) be the dose given to men with prostate cancer, although no evidence of cancer marker reduction was reported. Another trial gave high doses of an oral formulation of silybinin to six patients for an average of 20 days before having a prostatectomy. This study showed high peak blood concentrations, but low concentrations in prostate tissue when patients were examined after surgery. It was thought that perhaps a longer duration of therapy might be needed, or that the milk-thistle compound might work best when combined with chemotherapy. Despite the overall safety of milk thistle seen in these studies, there are still no clear data to suggest antitumour activity in patients with cancer.

Longer-term toxicology studies of milk thistle have not shown evidence of cancer promotion and side-effects for milk-thistle components in human beings are usually mild (they include

diarrhoea, gastrointestinal upset, and transiently raised concentrations of liver enzymes). Milk-thistle compounds might aff ect certain metabolic enzymes, including those that metabolise or breakdown drugs such as cytochrome P450, leading to interactions with other drugs, such as oral contraceptives, lipid-lowering agents (eg, statins), protease inhibitors (used to treat HIV and hepatitis C), and cancer chemotherapies. One problem has been its low absorption rates and rapid metabolism, and several groups are working on ways to improve these properties for clinical use.

Because milk thistle is categorised as a supplement, rather than a drug, it is not subject to the same oversight and quality control as standard drugs. Proportions of active compounds vary widely in different preparations, and there are several different compounds available on the market and internet even within oral formulations. Dosing has not been standardised, and there have been reports of contamination with mould, including aflatoxin, which is particularly concerning since it can cause liver cancer.

Besides these possible negative effects, compounds such as milk thistle could potentially be harmful in other ways. For instance, data from other antioxidants have shown that they might interfere with the efficacy of some cancer chemotherapy drugs by protecting cancer cells from cell death. It is not known if the same is true for milk-thistle compounds. Several studies have shown adverse effects of giving antioxidants to cancer patients, and it is likely that antioxidants work best when they fall within specifi c concentrations in cancer patients. This finding suggests that understanding appropriate doses and examining blood concentrations will be crucial for further development of milk-thistle compounds as anticancer therapies. Milk thistle has much to recommend it—it is well tolerated, and has clearly withstood the tincture of time. With better standardisation of formulations it could be transformed from a bitter pill to swallow to exciting seeds of change for the prevention and treatment of cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.