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

HerbClip™

File: ■ Milk Thistle (*Silybum marianum*)
■ Silymarin
■ Silybin
■ Cancer

HC 021026-404

Date: July 15, 2010

RE: Silymarin's Molecular Targets for Cancer Treatment and Prevention: a Review

Ramasamy K, Agarwal R. Multitargeted therapy of cancer by silymarin. *Cancer Letters*. 2008;269:352-362.

Accumulating evidence suggests that medicinal plants and their active phytochemicals may be used alone or in combination with traditional chemotherapeutic agents to treat or prevent cancer occurrence and metastatic spread. Specific phytochemicals are believed to suppress the inflammatory process leading to neoplastic transformation, promotion, and progression of carcinogenesis and angiogenesis. Silymarin, a flavonolignan complex from milk thistle (*Silybum marianum*) containing 65-80% silymarin flavonolignans (mainly silybin [syn. silibinin], isosilybin, silychristin, silydianin) with small amounts of flavonoids, and 20-35% fatty acids, has been traditionally used as a natural remedy for various liver conditions due to its antioxidative, anti-lipid peroxidative, anti-fibrotic, anti-inflammatory, immunomodulatory, and liver regenerating mechanisms. The authors of this review focus on investigations regarding silymarin's possible molecular targets for cancer prevention and treatment. Silymarin and its active compounds seem to act as possible cancer preventatives with different mechanisms involving all stages of carcinogenesis, initiation, promotion, and progression including modulation of cell cycle, anti-inflammatory activity, induction of apoptosis, anti-angiogenesis, anti-metastatic, and antioxidant activity.

Silymarin has been reported to suppress the proliferation of tumor cells in various cancers in vitro including prostate, ovarian, breast, lung, skin, and bladder, by inhibiting cell cycle progression at different stages. Studies have demonstrated that silymarin induces G1 arrest and/or G2-M arrest in human prostate cancer cells by causing an induction of cyclin-dependent kinase (CDK) inhibitors and a decrease in CDKs and associated kinase activities. Silybin treatment showed dose- and time-dependent growth inhibition together with G1 arrest in bladder transitional cell carcinoma (TCC), as well as growth inhibition of androgen-dependent and -independent prostate cancer cells. Silymarin has also been shown to induce G1 arrest through an increase in a CDK inhibitor and a decrease in kinase activity of CDK in human breast cancer cells. These studies suggested that regulation of cell cycle is one of silymarin's mechanisms of action in the prevention and therapeutic intervention of cancer.

Silymarin shows anti-inflammatory as well as anti-metastatic activity by modulating specific

proteins leading to the inhibition of transcription factor nuclear factor-κB (NF-κB), which regulates and coordinates the expression of interleukin (IL)-1 and -6, tumor necrosis factor (TNF)-α, lymphotoxin, granulocyte macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, and various other genes involved in inflammation, cell survival, differentiation, and growth.

Silymarin and/or silybin seem to modulate imbalance between cell survival and apoptosis through interference with the expression of cell cycle regulators and proteins involved in apoptosis. Studies have reported that silymarin exerts its anti-cancer effects by causing cell cycle arrest and inducing apoptosis in different types of cancers, such as CH11-treated human malignant melanoma, UV-irradiated human malignant melanoma (via SIRT1 activation leading to G2-M arrest), and leukemia cells (via inhibition of Akt activity).

The anti-angiogenic potential of silymarin/silybin has been demonstrated by its ability to decrease the secreted vascular endothelial growth factor (VEGF) levels in prostate and breast cancer cells, up-regulate VEGF receptor gene expression in human endothelial cells, and inhibit microvessel density and VEGF secretion in prostate and lung tumors. The anti-angiogenic effects of silybin have also been shown in terms of down-regulation of matrix metalloproteinase (MMP)-2 and CD34 in human hepatoma cell lines. These findings indicate the anti-angiogenic activity of silymarin and silybin in different cancers, which could be an important mechanism of their chemopreventive potential.

Silybin has been shown to act as an anti-invasive and anti-metastatic agent via down-regulation of specific MMPs, up-regulation of tissue inhibitor of metalloproteinase-2 (TIMP-2), and inhibition of activated protein (AP)-1-dependent MMP-9 gene expression. Since cancer metastasis depends on the motility and invasiveness of cancer cells, silybin represents a potential anti-metastatic agent due to its ability to suppress cancer cell invasion.

The free radical scavenging and antioxidant properties of silymarin and silybin could prevent or reduce chemotherapy-induced toxicity. Administration of silymarin increases the activities of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and glutathione-S-transferase, together with a decrease in the levels of malondialdehyde, a marker for lipid peroxidation, in erythrocytes exposed to H_2O_2. Silymarin reduces glutathione depletion, reactive oxygen species production, and lipid peroxidation in damage induced by UVA irradiation to human keratinocytes.

The efficacy of silymarin has been shown in vivo against chemically induced carcinogenesis, growth of tumor xenograft, as well as various transgenic models including UVB-induced photocarcinogenesis (via inhibition of cell proliferation, inflammation, and angiogenesis), advanced human prostate tumor xenograft growth (via anti-proliferative, pro-apoptotic, anti-angiogenic mechanisms), human non-small-cell lung carcinoma xenograft growth (via modulation of proteins involved in cell proliferation, inflammation, and angiogenesis), transgenic prostate adenocarcinoma (via modulation of CDKs, CDK inhibitors, insulin-like growth factor [IGF]-1, and IGF binding protein-3 expression), colon adenocarcinoma, ovarian cancer xenograft models, and renal cell carcinoma xenograft growth (via plasma level increase of IGF-1 binding protein). Mammary cancer prevention studies in mice were inconsistent. Overall, these in vivo studies strongly suggest the cancer chemopreventive efficacy of silymarin and/or silybin, and provide a strong rationale for their use in clinical trials.

Studies have demonstrated that silymarin may play a role in adjuvant cancer therapy: its use in cancer patients, either after or in combination with other chemotherapeutic agents, has been proven effective in treating chemotherapy-induced hepatotoxicity and protecting liver

during chemotherapy. Milk thistle supplementation in children with acute lymphoblastic leukemia (ALL) has been associated with a decrease in liver transaminase levels and greater than 50% reduction in total bilirubin. Oral administration of 5.1 mg/kg/day of Siliphos® (Indena S.p.A.; Milan, Italy), a silybin-phosphatidylcholine complex, exerted a protective effect on chemotherapy-induced hepatotoxicity in patients with ALL. In a nonrandomized study, patients with brain metastases receiving stereotactic radiotherapy with omega-3 fatty acids and silymarin had longer survival times and a decreased number of radionecroses. Silymarin (along with soy, lycopene, and antioxidants) was used in a phase III clinical trial after prostatectomy and radiotherapy to delay prostate-specific antigen progression in prostate cancer patients.

The in vivo effectiveness of silymarin depends on bioavailability and achieving therapeutic concentrations in the organs of interest. Silymarin's flavonolignans show poor water solubility and minimal bioavailability. To increase its bioavailability, silymarin was incorporated in a lipid-based self-microemulsifying drug delivery system (SMEDDS) and proved to be 1.88- and 48.82-fold more bioavailable than a solution or suspension of silymarin after intragastric administration to rabbits. Oral bioavailability of silybin was significantly higher and faster after Liverman capsule administration than after administration of Legalon® (Madaus GmbH; Koln, Germany) capsule or silymarin tablet in 24 healthy Korean male volunteers, who received a silybin dose of 120 mg in a 3x3 crossover study. Silybin shows significantly improved oral bioavailability when complexed with phosphatidylcholine as Siliphos (known in Europe as Silipide or IdB 1016; Indena S.p.A.; Milan, Italy). High levels of silybin were observed in the colorectal mucosa of patients with colorectal adenocarcinoma after oral administration of Silipide at doses of 360, 720, or 1440 mg daily for 7 days. This silybin phytosome (Siliphos) at a dose of 13 g, divided in three daily doses, appears to be well tolerated in patients with advanced prostate cancer, with free silybin initial plasma levels totaling over 100 μM.

This review summarizes silymarin's chemopreventive targets and mechanisms of action in various in vitro and in vivo models of cancer. These results validate silymarin's pharmacological safety and suggest its anti-cancer effects are exerted by multiple molecular mechanisms that could block carcinogenesis at all stages. The anti-invasive and anti-metastatic effects of silymarin validate its possible use as a preventive and therapeutic agent in more aggressive forms of cancer. Furthermore, silymarin has been clinically proven to reduce chemotherapy-associated toxicity when administered in combination with conventional chemotherapeutic agents. Additional clinical research is needed to further evaluate the chemopreventive and chemotherapeutic effects of silymarin and its analogues against various human cancers.

—Silvia Giovanelli Ris

Enclosure: Referenced article is available at:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2612997/pdf/nihms-72463.pdf (verified May 3, 2010).