Table 1: Controlled clinical trials of milk thistle (Silybum marianum) for side effects and toxicity during cancer treatment

Source: Ellen McDonell, Julia Green, Alexander Kalisch, CAM-Cancer Consortium. Milk thistle (Silybum marianum) [online document]. January 2019.

First author year (ref)	Study design	Participants	Interventions	Main outcome measures	Main results	Comments
Momeni 2015 [38]	RCT	60 adult patients with a diagnosis of cancer receiving cisplatin chemotherapy	Treatment group: Silymarin tablet 140mg bid for 7 days before cisplatin administration + Cisplatin Control: Cisplatin only	Nephrotoxicity as measured by Blood urea nitrogen (BUN) and serum creatinine. Blood samples taken on day 0 (cisplatin administration day), day 3, and day 14	Lower BUN and serum creatinine 2-weeks after cisplatin administration in treatment group compared to control BUN: 14±4.2 vs 18±8.8, P=0.027 Creatinine: 0.80 mg/dL±0.19 vs 1.0 mg/dL±0.26, P=0.001 No significant difference between groups at day 0 or day 3.	No placebo control, no discussion of types of cancer the individuals were being treated for, short-term follow up of study, blinding not mentioned.
Shahbazi 2015 [39]	RCT, pilot	24 patients with mixed cancer diagnoses receiving cisplatin-based chemotherapy	Treatment: Silymarin 420mg daily in three divided doses starting 24-48 hours before cisplatin initiation until the end of three-21 day cisplatin cycles Control: placebo tablets and cisplatin-based chemotherapy	Renal function, renal electrolyte wasting	No difference between groups on incidence of acute kidney injury, urinary magnesium and potassium wasting. Silymarin was safe, no AEs	Samples were taken once daily following cisplatin-administration until patient was discharged from hospital (which occurred within 4 days). Cisplatin AEs may occur >4 days after administration and thus not have been detected.
Ladas 2010 [31]	RCT, pilot, multi-centre	50 children with ALL and hepatotoxicity being treated with chemotherapy	Treatment: oral milk thistle (MT) at 5.1mg/kg/day for 28 days + chemotherapy Control: placebo + chemotherapy	Hepatic function measured by liver toxicity	No significant different between groups at 28 days. AST significantly reduced at day 56 (P = 0.05) and trend towards lower ALT (P = 0.07) in treatment group compared to control. No difference between groups in side effects, toxicities, infections MT did not antagonize the effects of chemotherapy agents	Multi-centred pilot trial, groups were well matched and all participants accounted for. The placebo was indistinguishable from milk thistle in appearance and odour.

Hagag 2016 [40]	RCT	80 children with newly diagnosed ALL, 4-13 years of age	Treatment: Silymarin 420mg/day in 3 divided doses for 1 week following each methotrexate (MTX)-based chemotherapy treatment Control: Placebo for one week following MTX-based chemotherapy	Hepatic and renal toxicity following chemotherapy Hepatic function: Serum bilirubin, total proteins, albumin, globulin and albumin-globulin ration, ALP, ALT, AST, prothrombin time Renal function: BUN, serum creatinine, serum cystatin C, urinary N-acetyl-beta-D-glucosaminidase	Significantly higher ALT, AST, ALP, and significantly lower prothrombin activity in placebo group compared to silymarin group. Significantly lower BUN, creatinine, cystatin C and urinary N-acetyl-beta-D-glucosaminidase in silymarin compared to placebo group. Silymarin improved several hepatic and renal function markers in children with ALL treated with MTX-based chemotherapy.	
Hagag 2018 [41]	RCT	80 children with ALL 40 in control group, 40 in treatment group	Treatment: Silymarin 420mg for 1 week following each doxorubicin infusion Control: Placebo for 1 week following each doxorubicin infusion	Cardiotoxicity measured by Echo-Doppler measurements of left ventricular (LV) systolic and diastolic function, and pulsed wave tissue Doppler of lateral mitral annulus	Significantly greater reduction in systolic function (EF, FS, S wave) in control group compared to silymarin group after doxorubicin therapy, serum troponin rise following doxorubicin was significantly lower in silymarin group compared to placebo group.	Only the abstract was reviewed for this paper, cannot critically evaluate or comment sufficiently on limitations
Mohaghegh 2015 [42]	RCT	99 patients with invasive breast cancer receiving chemotherapy (Doxorubicin, epirubicin, cyclophosphamide, docetaxel, paclitaxel)	Treatment: 70mg silymarin 3x/day Control: placebo tablet Both groups received taxane-containing chemotherapy (Doxorubicin, epirubicin, cyclophosphamide, docetaxel, paclitaxel)	Hepatic function	Significantly higher levels of AST in the control group compared to the silymarin group after the 4th taxane and 1 month after chemotherapy ($p < 0.05$). Significantly higher levels of ALT after the 3rd and 4th taxane, and 1 month after the end of chemotherapy for ALT ($p < 0.05$). No statistically significant differences between groups for ALP, total or indirect bilirubin.	Magnitude of effect may not be clinically relevant. Larger studies and possibly larger doses of silymarin are recommend to evaluate the impact.

Table continued

Elyasi 2016 [44]	RCT, pilot	27 patients with head and neck cancer being treated with radiation therapy	Treatment: Silymarin 420mg daily in three divided doses starting on day 1 of radiotherapy for 6 weeks Control: Placebo tablets with radiotherapy	Radiation-induced mucositis as measured weekly by World Health Organization and National Cancer Institute Common Terminology Criteria (NCICTC and CTCAE respectively)	Median WHO CTCAE and NCICT scores were significantly lower in the silymarin group at the end of each week (week 1-6) compared to the placebo group ($p<0.05$). Mucositis development was delayed in the silymarin group and decreased the severity. Treatment well tolerated, no AEs attributed to silymarin.	Small sample size
Elyasi 2017 [45]	RCT, pilot	40 patients with gastrointestinal cancers being treated with capecitabine chemotherapy	Treatment: Silymarin gel 1% applied to palms and soles twice daily starting with first day of chemotherapy (capecitabine + oxaliplatin) for 9 weeks Control: placebo gel with similar colouring applied same as the treatment group during chemotherapy (capecitabine + oxaliplatin)	Hand-Foot Syndrome (HFS) as measured by WHO HFS score, evaluated every 3 weeks for 9 weeks	Median HFS score was significantly lower in silymarin group at the end of the 9th week of treatment compared to the placebo group ($p<0.05$). There was no statistically significant differences between groups at week 3 or 6. Silymarin gel was well tolerated, no AEs	Small sample size. Short-term follow up (9 weeks)
Becker-Scheibe 2011 [34]	Non randomized, prospective observational trial	101 patients receiving adjuvant radiotherapy following breast cancer surgery	Treatment: topical silymarin-containing cream (Liviaderm) Control: standard of care	Acute skin reaction according to Radiation Therapy Oncology Group (RTOG) scale and visual analogue scale (VAS)	Median time to toxicity was significantly longer in Liviaderm group (45 vs 29 days, $p < 0.0001$)	Non-randomized, observational trial increases potential for bias