Table 1: Controlled clinical trials of milk thistle (*Silybum marianum*) for adverse events and toxicity during cancer treatment

Source: Dana Mora, Ellen Conte, CAM-Cancer Collaboration. Milk thistle (Silybum marianum) [online document]. January 2024.

First author Year	Study design	Participants	Interventions	Main outcome measures	Main results	Comments
Chemotherapy-induced hepatotoxicity						
Ladas 2010	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	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.	

Ghazizadeh 2021	Double blinded RCT	90 children with ALL	Treatment: 7 mg/kg milk thistle daily Control: Placebo pill	Hepatotoxicity measured by serum level of AST and ALT	At day 35 and day 70 of the study, in the milk thistle arm ALT and AST mean serum levels were lower than the placebo group ($P<0.001$).	
Mohaghegh 2015	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.
Mshemish 2011	open label RCT	74 patients with breast cancer	Intervention 1: CAF treatment and 210 mg per day for 63 days Intervention 2: CAF treatment and 420 mg per day for 63 days Control: received the normal CAF protocol once every 21 days for 63 days.	Indices of liver function (AST, ATL, TSB) were measured at day 21, 42, and 63	Levels of AST and ALT showed significant reduction when silymarin used with CAF protocol, in a time and dose-dependent manner. TSB levels significantly reduced by CAF protocol but does not show any significant change after treatment with silymarin.	
Moezian 2022	Triple blinded RCT	20 non-metastatic breast cancer patients receiving adjuvant chemotherapy with dose dense AC-T regimen	Treatment: silymarin tablets (140 mg) three times a day with meals Control: placebo tablets three times a day with meals	Hepatotoxicity: presence of FL, serum level of AST, ALT, direct and indirect bilirubin, alkaline phosphatase (ALP), prothrombin time (PT), creatinine (Cr), and the blood urea nitrogen.	There was a non-significant trend toward more severe liver involvement in placebo group comparing to the silymarin group after intervention based on ultrasonography	The study had a small sample size.

Chang 2021	RCT	70 metastatic colorectal cancer adult patients receiving first-line systemic therapy with FOLFIRI plus bevacizumab	Treatment: Silymarin for a duration of 7 days, and the dose of silymarin was 150 mg 3x /day. Control group: FOLFIRI plus bevacizumab only	Incidence of gastrointestinal (GI) toxicities. The secondary endpoints were median progression-free survival (PFS) and overall survival (OS) of these patients.	The treatment group experienced less AEs in diarrhea (5.7% vs. 14.6%, p=0.002) and nausea (27.0% vs. 40.2%, p= 0.005) in comparison with the control group, but no significant differences in hepatic toxicities were observed.	The study was not blinded.
Chemotherapy-induced nephrotoxicity						
Momeni 2015	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	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.

Chemotherapy-induced cardiotoxicity						
Hagag 2019	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 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.
Zalat 2020	RCT	83 patients diagnosed with cancer and receiving anthracycline chemotherapy	1. 3 mg capsules of l-carnitine one day before the chemotherapy cycle and 1 mg during the following 21 days. 2. 140mg silymarin once daily during the chemotherapy cycle. The treatment period was 6 months. 3. Control no additional treatment to chemotherapy.	Cardiotoxicity Blood sample was collected to measure LDH, CK-MB, cTn I, Anticardiolipin IgG, Fe, ferritin, and TIBC and % of saturation. % EF	The supplementation with silymarin to anthracycline chemotherapy had a statistically significant decrease in Anticardiolipin IgG (P=0.000), iron (P=0.001), ferritin (P= 0.001), TIBC (P=0.007), and % saturation (P=0.001). Silymarin group showed a significant decrease in iron profile compared to the l-carnitine group.	The authors do not state if the study was blinded furthermore, they do not indicated what the protocol was to treat the control group.

Chemotherapy-induced mucositis						
Altaei 2012	Double-blinded RCT	65 cancer patients with radiotherapy induced mucositis	Treatment 1: 140mg /cap of silymarin Control 1: received 25 mg/cap of Indomethacin Control 2: placebo daily for 14 days	Mucositis was measured using the Oral Mucositis Assessment Scale (OMAS) and World Health Organization score (WHO)	Significantly lower OMAS and WHO scores in those who took silymarin compared to the other groups	
Elyasi 2016	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
Hosseini 2021	Double blinded RCT	31 adult patients diagnosed with head and neck cancer undergoing radiotherapy	Treatment: 5 mL of nano-solution three times daily with meals which is started from the first day of radiotherapy and continued for 6 weeks Control: 5 mL of placebo solution	Severity of mucositis Level of serum creatinine and blood urea nitrogen (BUN) and liver enzymes were assessed weekly.	The median EORTC scores were not significantly different between silymarin and placebo groups at the end of the sixth week ($p > 0.05$). However, after 4 weeks of treatment with silymarin, the scores had a non-significant decreasing trend in contrast to placebo group.	The study had a small sample size.

Radiation dermatitis						
Becker-Schiebe 2011	Non random-ized, prospec tive observa tional 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. Combination product.
Karbasforoo shan 2019	Double-blind RCT	40 adults breast cancer patients with planned course of post mastectomy	Treatment: silymarin 1% gel /day for 5 weeks Control: placebo gel for 5 weeks	Radiodermatitis occurrence at the beginning of RT and at weekly intervals for 5 weeks.	Significantly increased scores in both placebo and silymarin groups during radiotherapy, but radiodermatitis development and progression was delayed in silymarin group.	Small sample size.
Chemotherapy-induced hand-foot syndrome						
Elyasi 2017	RCT, pilot	40 patients with gastrointestinal cancers being treated with capecitabine + oxaliplatin chemotherapy	Treatment: Silymarin gel 1% applied to palms and soles twice daily starting with first day of chemotherapy for 9 weeks Control: placebo gel with similar colouring applied as in the treatment group	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)