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The hepatorenal protective effects of silymarin in cancer patients receiving chemotherapy: a randomized, placebo-controlled trial

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Abstract

Background Breast cancer is one of the most common diseases globally that may have side effects on liver and renal function. Pharmacological treatments to reduce adverse liver and renal effects are still limited. It has been proposed that silymarin may possess hepatoprotective and anti-inflammatory properties. The present trial aims to assess the hepatorenal protective efficacy of silymarin supplementation in cancer patients receiving chemotherapy in an outpatient setting.

Method This is a randomized, placebo-controlled clinical trial that recruited female breast cancer patients. Participants were randomly assigned to one placebo group and two intervention groups. The control group received 140 mg of placebo daily, while the two intervention groups received 140 mg silymarin daily. Follow-up assessments were conducted at baseline, 3 weeks, and 6 weeks. At the beginning of the study, the patients were subjected to a computed tomography (CT) scan, and the liver and renal parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, Blood urea nitrogen (BUN) and Creatinine (Cr) were examined through laboratory tests.

Results Despite two deaths and three dropouts, 100 patients completed the study. Silymarin showed significant effects on liver enzymes in the levels of ALP and bilirubin ($P < 0.05$), with no significant impact on renal function in the levels of Blood urea nitrogen (BUN) and Creatinine (Cr) ($P > 0.05$). The medication was well-tolerated, with minimal reported side effects ($P > 0.05$).

Discussion The study suggests that silymarin may have hepato-renal protective potential in breast cancer patients and improve patient tolerance to chemotherapy. The data presented on the efficacy and safety of silymarin may provide stronger foundation for further trials and for a possible use in clinical practice.

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Keywords Silymarin, Chemotherapy, Outpatient, Cancer patients, Liver and renal injury

Introduction

Cancer is one of the common chronic and non-communicable diseases that account for 9% of deaths worldwide [1]. In advanced countries, it is the second leading cause of death after cardiovascular diseases and it ranks as the fourth leading cause of death in developing countries [2]. In total, 50 million deaths occur annually worldwide, with over 5 million attributed to cancer [3]. According to published statistics, the death rate from cancer in Iran was 66.92 per 100,000 people each year [4]. The prevalence of cancer is increasing, with factors such as global population aging, increased risk behaviors, especially smoking, exposure to stimulants like chemicals and radiotherapy [5], inappropriate dietary habits, and sedentary lifestyles contributing to this rise [6, 7].

Various techniques are used to predict and treat cancers, including chemotherapy, radiotherapy, surgery, hormone therapy, immunotherapy, biological therapies, cryotherapy and artificial intelligence [8–12]. These treatments can last for weeks or months, significantly impacting a patient's quality of life [13]. On the other hand, chemotherapy drugs are generally associated with various side effects. The most common of these side effects include nausea, vomiting, diarrhea, hair loss, darkening of the skin and nails, bone marrow suppression, mucositis, ovarian dysfunction, hyperuricemia, neuropathy, cardiomyopathy, hemorrhagic cystitis, renal and hepatic issues, and electrolyte imbalances [14–16]. A study in the United States has shown that 22 FDA-approved cancer drugs between 2000 and 2002 were associated with 25 serious adverse effects [17]. Paclitaxel and docetaxel are new class spindle inhibitor drugs that prevent mitosis. The mechanism of action is through microtubules. These two drugs have been associated with an increase in aminotransferase levels in 7 to 26% of cases and mild elevation in bilirubin levels, as well as causing hepatotoxicity in 5 to 20% of cases, which is usually asymptomatic and self-limiting due to the direct effect of the drug [18, 19].

Extensive studies have been conducted to evaluate the protective effects of various chemical compounds in reducing the toxic effects of chemotherapeutic drugs on the liver [20, 21]. However, some compounds used as chemoprotectors to reduce the adverse effects and toxicity in therapeutic methods may decrease their anticancer effects, while others do not completely eliminate the toxic effects of these drugs [22]. On the other hand, biologically derived plant-based substances, which constitute a branch of modern pharmacotherapy for diseases, have very minimal side effects in patients [23–25]. Therefore, the search for natural products in this field is of particular clinical importance. In recent years, the development of new plant-derived antioxidants to overcome damage caused by toxic chemical factors has been a serious focus for researchers [26]. Antioxidants are substances that, even in small amounts, can protect the body against various oxidative damages caused by reactive oxygen species [27].

In recent decades, a variety of dietary and herbal supplements have been traditionally used alongside some industrial drugs and non-steroidal anti-inflammatory drugs to control and modify undesirable symptoms and indicators of many diseases [28, 29]. Therefore, the results of some studies suggest that the herbal medicine Silybum marianum (Milk Thistle), also known as Mary Thistle or Holy Thistle, as a member of the daisy or aster family native to the Mediterranean region, has clinically significant effects in treating many metabolic diseases in modern medicine [30–32]. Researchers highlight the importance of the main methanolic extract of Milk Thistle seeds, namely Silymarin with the chemical formula $C_{25}H_{22}O_{10}$, as the main effective flavonoid for pharmacological and physiological purposes [31, 32]. Silymarin is a complex mixture of polyphenolic molecules, including seven related flavonolignans such as Silybin A, Silybin B, Isosilybin A, Isosilybin B, Silychristin, Isosilychristin, and Silidianin, and a flavonoid called Taxifolin [33]. Clinical studies have shown that Silymarin, particularly Silybum as a Major Bioactive Component of Milk Thistle [34, 35], due to its antioxidant, anti-inflammatory, antifibrotic, hepatocyte-regenerating, and immune system-regulating properties, is widely used for the treatment of various liver diseases (such as cirrhosis, carcinoma, hepatitis, and fatty liver), diabetes, atherosclerosis, cancer, osteoporosis, and for the regulation of lipids and blood sugar [36–38].

Nowadays, Silymarin is utilized in in managing a broad spectrum of diseases including liver dysfunctions (fatty liver, hepatitis, jaundice, alcohol-induced liver damage, ischemia, drug and environmental toxicities, and even liver fibrosis) [39], cancers, neurological diseases, parasitic and infectious diseases, and metabolic disorders [40, 41]. Silymarin can reduce the levels of free radicals such as hydroxyl, superoxide, and hydrogen peroxide, increase the stimulation of glutathione production and enhance the activity of superoxide dismutase enzymes, leading to the prevention of lipid peroxidation, maintenance of cell membrane integrity, prevention of leakage of intracellular enzymes, and consequently reducing liver tissue damage. Additionally, by inhibiting the NF-κB gene and subsequently reducing the production of pro-inflammatory cytokines from the liver, Silymarin protects against damage [42, 43]. Furthermore, Silymarin is involved in

preventing liver-related damage by inhibiting phosphatidylcholine synthesis and protein and RNA simulation [44].

The preventive and anticancer effects of silymarin have been confirmed and well-documented in many studies. However, its hepatorenal protective effects have been limitedly investigated in cancer patients, particularly those with breast cancer [45]. Kakar et al. have demonstrated that a one-month treatment with silymarin (140 milligrams three times a day) among 30 breast cancer patients without any metastasis can significantly reduce severity of hepatotoxicity in patients undergoing treatment with doxorubicin/cyclophosphamide-paclitaxel (AC-T) regimen [46]. A study conducted by Mohaghegh et al. to investigate the effect of silymarin on reducing hepatic side effects of taxanes in breast cancer patients undergoing chemotherapy with taxane-containing regimens divided patients into two treatment groups and a placebo group, showed that although there was a significant difference between the two groups after the study, the changes in the intervention group before and after treatment were not significant [21]. Another study by Hangag et al. in children with acute lymphoblastic leukemia undergoing chemotherapy with methotrexate, silymarin therapy improved some liver function indicators such as ALT, AST, and ALP, while albumin and bilirubin levels did not differ between the treatment and control groups [47]. Studies also highlight the hepatorenal protective effects of silymarin through its anti-inflammatory, anti-apoptotic, and antioxidant properties, as well as its capacity to prevent oxidative stress and pathological tissue changes caused by chemotherapy-induced damage [48, 49].

The importance of using silymarin as a complementary or non-toxic drug in improving the function of various cancer, kidney and liver groups has been highlighted. However, limited studies have focused on the hepatorenal protective effects of silymarin on breast cancer patients undergoing chemotherapy. Therefore, proactive evaluation of silymarin on the health performance of cancer patients undergoing chemotherapy with the aim of improving quality of life and increasing tolerance to chemotherapy is essential, given the importance of preventing liver damage in the treatment process of cancer patients. This randomized controlled clinical trial, with a parallel drug-controlled group, can help improve treatment performance methods, increase the effectiveness of chemotherapy in breast cancer patients and play a significant role in improving patient health by identifying and determining the protective potential of silymarin. Therefore, the main objective of this study was to evaluate the hepatorenal protective efficacy of silymarin supplementation in cancer patients receiving chemotherapy, with the hypothesis that silymarin supplementation leads to improved liver and renal function test results compared to placebo.

Method: participants, interventions, and outcomes

Study design

This study is a randomized, parallel-group, placebo-controlled clinical trial conducted to investigate the preventive effect of silymarin (livergel) on hepatorenal damage caused by chemotherapy in cancer patients referred to affiliated outpatient clinics of an academic institution with chemotherapy indications in 2021. To perform interventions and collect data, after the study protocol was approved by the Medical Ethics Committee (First Trial Registration: 16/08/2021, Registration Number: IRCT20201123049474N2), patients meeting the inclusion criteria completed informed consent forms to participate in the study. The informed consent form included elements such as the introduction of the research, the procedures involved, the manner of participation, benefits and potential side effects, costs, alternative methods, confidentiality of information, the researcher's accountability to answer queries, the right to decline or withdraw from the study, and the affirmation of the consent form. After determining the required sample size for each group and identifying breast cancer patients without hepatic metastasis, a randomization method (using computer-generated random numbers) was employed to allocate patients to each group, and 35 individuals were recruited per group. Initially, encompassing detailed of patient demographics, medical history, and clinical outcomes were collected, and after the intervention, data were reassessed following a 60-day period. The study flowchart is shown in Fig. 1. Data collection was conducted by a trained researcher following approved protocol. A clinical trials expert verified and confirmed the collected data to ensure its accuracy and validity. A secure and centralized data repository was established with restricted access to maintain confidentiality and data integrity.

Sample size

The sample size was calculated based on the equation for comparing means in at least two groups using SPSS 26.0 software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Considering the assumption of equal variances, a minimum of 10% dropout rate, study power of 80% with a statistical significance level (α) of 95% ($P=0.05$), a sample size of 35 individuals per group was determined, resulting in a total sample size of 105 individuals in the current study (Eq. 1).

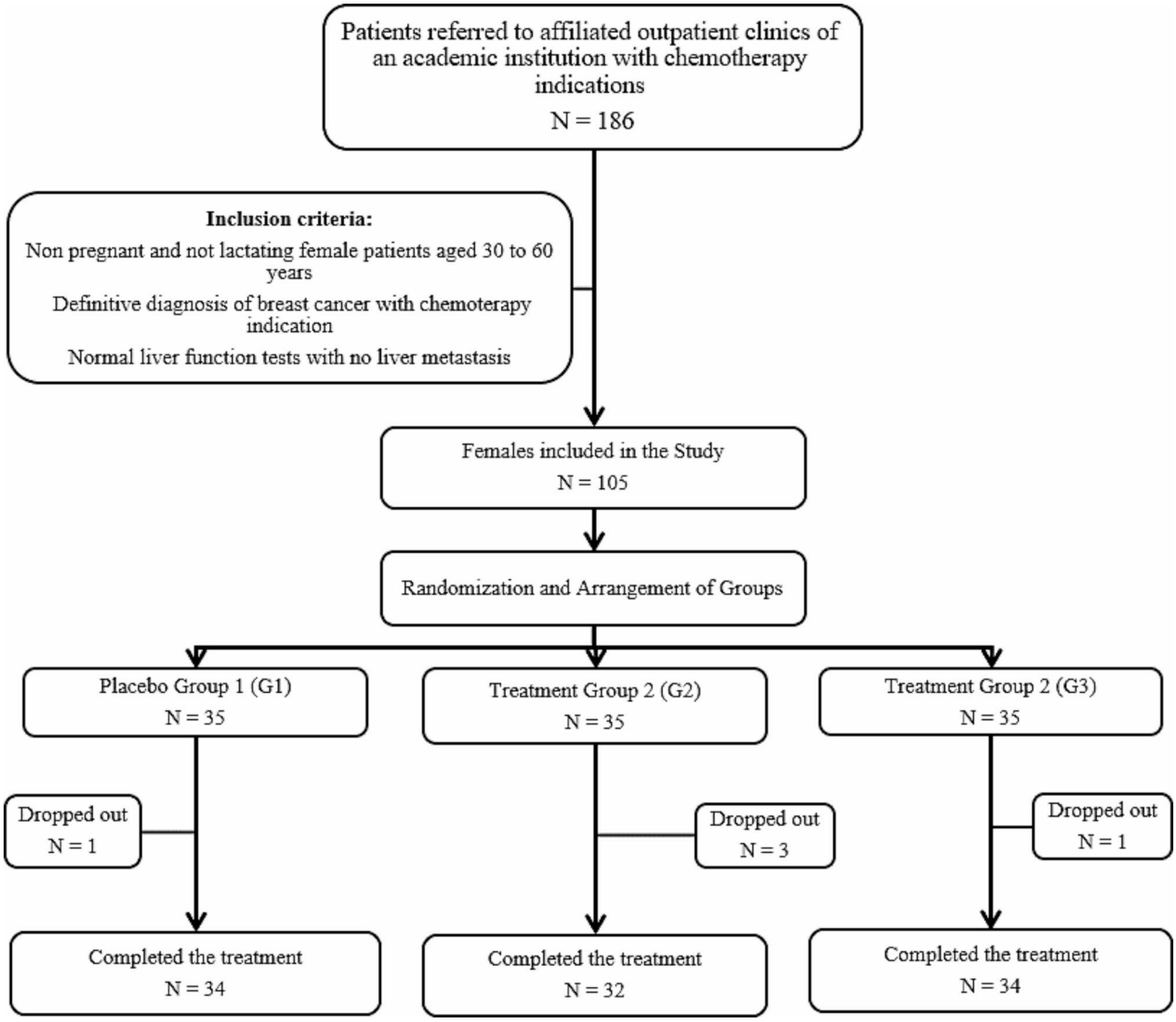

Fig. 1 Study design and flowchart

$$\text{N Per group} = 2\times\frac{\left[Z\left(1-\frac{\alpha}{2}\right)+Z\left(1-\beta\right)\right]^2\times SD^2}{d^2} \quad (1)$$

Where $Z(1-\frac{\alpha}{2})=1.96$, α=0.05, β=0.2, d=0.7 SD

After calculating the sample size, patients who met the study inclusion criteria were selected using simple random sampling method and allocated into three groups (placebo, treatment 1, and treatment 2) in a 1:1 ratio based on random allocation generated by a biostatistician using a computer-generated random number table inside the clinic.

Eligibility criteria

Inclusion and exclusion criteria

Inclusion criteria for the study included female patients aged 30 to 60 years, ability to take oral medication, definitive diagnosis of breast cancer with indication for chemotherapy but not yet received chemotherapy, normal liver function tests before intervention, indication for treatment with chemotherapy regimen, non-pregnant and not lactating, absence of liver metastasis (except stage 4) and liver disease. Exclusion criteria also included patient death, pregnancy during the study, patients who were unwilling to continue and cooperate in the study.

Interventions

Following determining the sample size in each group, researchers identified patients by attending the clinic. Initially, patients with breast cancer who had been visited by an oncology specialist and met the indication for chemotherapy and study entry criteria were informed consented, and the study objective was explained. To this end, patients underwent an initial computed tomography (CT) scan at the beginning of the study to confirm the

absence of hepatic metastasis based on the initial assessment results. Subsequently, using a two-part checklist including demographic information such as age, and basic clinical information such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, Blood urea nitrogen (BUN) and Creatinine (Cr), all patients were collected. After assigning individuals to the relevant intervention and control groups, each group received two tablets daily (total of 120 tablets) for 60 days during the study period. The control group (G1) received a placebo, while treatment groups 1 (G2) and 2 (G3) received silymarin. The control group received two placebo tablets daily, treatment group 1 received two tablets of 140 mg silymarin daily cycle simultaneously with the start of the first chemotherapy cycle, and treatment group 2 received two tablets of 140 mg silymarin daily one week before the start of the first chemotherapy for two months.

The control group also received placebo tablets daily for two months starting with the first chemotherapy cycle. Liver and renal enzymes were re-evaluated at three time points (0, 3, and 6 weeks) during the study by a reliable laboratory that was unaware of the study and groups. Furthermore, participants were provided with information about the study drug, such as a drug information brochure, in accordance with local procedures, and a drug diary card for recording their weekly consumption. In case of missing a dose, participants were instructed not to take the medication unless 3±days had passed from the scheduled date. face-to-face consultations every two weeks and monthly Telephone contact were carried out for all participants. Finally, after completing the intervention period, a brief telephone counseling session was conducted to discuss the side effects of the drug taken and improvements in the participants' health conditions.

Statistical analysis

After collecting the relevant data, the information was entered into the software. Continuous and categorical variables were reported as mean±standard deviation (SD) and frequency (percentage). Normality of continuous data was evaluated using Kolmogorov-Smirnov test and Q-Q plot. categorical data were compared between three groups using chi-squared test. Repeated measures analysis of variance was used for evaluating within and between groups compassions in terms of liver enzymes and nephrological indices. Sphericity assumption was evaluated by using Muchly test and when it was violated, the multivariate analysis of variance adopted for data analysis. We also compared three groups in each study time point by using one-way analysis of variance (ANOVA) along with Bonferroni correction for multiple testing [50]. All statistical analyses were conducted using SPSS version 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). A statistical significance level of *P*-Value<0.05 was considered for all analyses.

Results

During the period of this clinical trial study, totally 105 female patients with breast cancer were screened and recruited for the trial, of whom 35 patients in placebo group 1 (G1), 35 patients in the silymarin group 2 (G2), and 35 patients in the silymarin group 3 (G3). During the study, two individuals died due to a heart attack (Group G2) and a pulmonary embolism (Group G3). Three individuals also dropped out due to the recommendation of their relatives not to use herbal medication (Group G1), experience severe nausea and vomiting (Group G2), and reading the drug information leaflet and being aware of the side effects of the drug (Group G2). they discontinued medicine use and were not willing to continued cooperation. Ultimately, 100 patients completed the study (Fig. 1).

The minimum age in G1 and G3 groups was 28 years, and the maximum age was 60 years, while the minimum and maximum age in the G2 group was 33 and 60 years, respectively. The mean age of patients in G1 group was 48.74±8.06 years, in G2 group was 52.09±7.35 years, and in G3 group was 48.51±8.85 years. There was no statistically significant difference among the three groups in terms of age and $P=0.125$ indicated that the three groups were approximately equal in age.

The level of liver enzymes in three different periods in the intervention and control groups has been presented in Table 1. Mean change of AST over study period was significant in group G3 ($P=0.01$), and marginally significant in group G2 ($P=0.059$). Also, it was not significant in group G1 ($P=0.143$). However, there was no significant difference between three groups both generally ($P_{Group}=0.216$) and each time point ($P>0.01$ for all three time points). The trend of changes in three groups for AST was similar ($P_{Time*Group}=0.414$). Mean change of ALT over study period was significant in group G2 ($P=0.007$), and group G3 ($P=0.039$). However, there was not significant different in group G1 ($P=0.277$). Also, there was no significant difference between three groups both generally ($P_{Group}=0.599$) and each time point ($P>0.01$ for all three time points). The trend of changes in three groups for ALT was similar ($P_{Time*Group}=0.063$).

Mean ALP period showed significant change over study in group G2 ($P_{Time}=0.001$), and group G3 ($P_{Time}=<0.001$). However, it was not significant difference in group G1 ($P_{Time}=0.324$). Three groups showed significant difference overly in terms of changes in this variable ($P_{Group}=0.001$) and the difference between three groups was significant at 6 weeks in which the mean

Table 1 Comparison of liver enzymes among different groups of silymarin recipients and placebo at various times

Liver enzymes	Intervention Groups	Time			P_{Time}	P_{Group}	$P_{T*Group}$	Effect size**	Observed power**
		1 (0th week)	2 (3th week)	3 (6th week)					
AST (U/l)	G1	19.32 ± 4.30	20.71 ± 5.97	19.5 ± 9.45	0.143	0.216	0.414	0.03	0.32
	G2	20.72 ± 5.39	24.63 ± 12.53	22.5 ± 9.85	0.059				
	G3	20.88 ± 5.74	24.53 ± 12.61	21.94 ± 9.57	0.01				
	*P**	0.390	0.241	0.402					
ALT (U/l)	G1	18.89 ± 3.46	21.56 ± 9.63	20.68 ± 6.63	0.277	0.599	0.063	0.01	0.13
	G2	17.87 ± 3.37[a]	27.16 ± 15.47[a]	20.97 ± 7.88	0.007				
	G3	18.79 ± 3.41	21.03 ± 12.88[a]	20.88 ± 7.91	0.039				
	*P**	0.590	0.212	0.987					
ALP (U/l)	G1	172.5 ± 35.77	172.65 ± 30.84	166.53 ± 20.23	0.324	0.001	< 0.001	0.13	0.94
	G2	193.62 ± 42.80[a]	189.06 ± 37.31[a]	206.47 ± 35.65	0.001				
	G3	187.76 ± 37.20[a]	185.47 ± 35.57[a]	217.85 ± 38.69	< 0.001				
	*P**	0.14	0.188	< 0.001					
Bilirubin (U/l)	G1	0.72 ± 0.17	0.72 ± 0.16	0.70 ± 0.17	0.57	0.314	0.046	0.02	0.25
	G2	0.75 ± 0.17	0.78 ± 0.13	0.77 ± 0.16	0.55				
	G3	0.71 ± 0.18 [a]	0.71 ± 0.18 [a]	0.77 ± 0.14	0.042				
	*P**	0.752	0.186	0.116					

Data are reported as mean ± SD, AST = Aspartate transaminase; ALT = Alkaline transaminase; ALP = Alkaline phosphatase; Bili: Bilirubin, G1: placebo group, G2: Receiving silymarin at the start of the first cycle of chemotherapy, G3: Receiving silymarin one week before starting the first chemotherapy. * From one-way ANOVA, P_{Time}, P_{Group} and $P_{T*Group}$ resulted from repeated measures ANOVA

a: indicating significant difference from time 3. ** effect size and observed statistical power were reported for comparing interventions

Table 2 Comparison of nephrological parameters among different groups of silymarin recipients and placebo at various times

Nephrological Parameters	Intervention Groups	Time			P_{Time}	P_{Group}	$P_{T*Group}$	Effect size**	Observed power**
		1 (0th week)	2 (3th week)	3 (6th week)					
BUN	G1	13.80 ± 2.78	13.32 ± 2.58	13.53 ± 2.03	0.131	0.484	0.677	0.015	0.17
	G2	14.28 ± 2.59	14.06 ± 2.12	14.12 ± 1.88	0.722				
	G3	14.09 ± 2.66	13.79 ± 2.09	14.09 ± 1.96	0.248				
	*P**	0.579	0.412	0.381					
Cr	G1	0.86 ± 0.21	0.87 ± 0.18	0.86 ± 0.17	0.762	0.340	0.081	0.02	0.24
	G2	0.82 ± 0.22	0.87 ± 0.19	0.86 ± 0.17	0.217				
	G3	0.82 ± 0.20	0.80 ± 0.18	0.80 ± 0.17	0.396				
	*P**	0.529	0.145	0.264					

Data are reported as mean ± SD, BUN = Blood urea nitrogen; Cr = Creatinine; G1: placebo group, G2: Receiving silymarin at the start of the first cycle of chemotherapy, G3: Receiving silymarin one week before starting the first chemotherapy. *From one-way ANOVA, P_{Time}, P_{Group} and $P_{T*Group}$ resulted from repeated measures ANOVA. ** effect size and observed statistical power were reported for comparing interventions

ALP in this time point in groups G2 and G3 was significantly higher than G1 ($P<0.001$). The trend of changes show similar patterns over time in three groups for ALP ($P_{Time*Group}<0.001$). Furthermore, Mean bilirubin period indicated significant change over study in group G3 ($P_{Time}=0.042$). However, there was not significant difference in group G1 ($P_{Time}=0.57$), and group G2 ($P_{Time}=0.55$). Also, there was no significant difference between three groups both generally (PGroup = 0.314). However, the trend of bilirubin changes among three groups after a period of 6 weeks was significant (PTime*Group = 0.046). These findings demonstrate that silymarin's hepatoprotective effects on breast cancer patients are notable in certain parameters, such as ALP and Bilirubin, potentially leading to improved liver function.

Furthermore, the laboratory test results of two parameters, BUN and Cr, were compared among the three groups after administration of silymarin and placebo (Table 2). The Mean change of BUN and Cr over study period was not significant among any of the groups ($P>0.05$). Also, there was no significant difference between the three groups both in general ($P_{Group}>0.05$) and each time point ($P>0.05$ for all three time periods). However, the trend of changes in three groups for BUN and Cr were similar ($P_{Time*Group}=0.414$). These findings indicate that the renal protective effect of silymarin on breast cancer patients was not considerable and did not result in any significant changes.

The results of the assessment of medication and chemotherapy side effects among three groups are showed in Table 3. Only one individual in Group G2 reported

Table 3 Comparison of medicine and chemotherapy side effects among different groups of silymarin recipients and placebo

Intervention Groups	Chemotherapy side-effects			Medicine side-effects		
	No	Yes	*P**	No	Yes	*P**
G1	25(78.1%)	7(21.9%)	0.384	32(100%)	0(0%)	0.353
G2	20(62.5%)	12(37.5%)		31(96.9%)	1(3.1%)	
G3	23(67.6%)	11(32.4%)		34(100%)	0(0%)	

Data are reported as frequency (percentage), G1: placebo group, G2: Receiving silymarin at the start of the first cycle of chemotherapy, G3: Receiving silymarin one week before starting the first chemotherapy. *Obtained from chi-squared test

medication side effects (3.1%). The chemotherapy side effects reported in Group G2 (12%) were higher compared to the other groups. However, the reported side effects among the groups did not show a significant difference ($P>0.05$). Therefore, silymarin has not shown significant toxicity or drug interactions among patients and is considered safe for medicinal use.

Discussion

Breast cancer is one of the most common malignancies, especially among women worldwide. According to statistics in 2020, more than 2.3 million cases of breast cancer were reported globally [51]. Various studies have shown a high incidence of functional disorders and hepatotoxicity in cancer patients undergoing chemotherapy [52, 53]. Medications and agents used in cancer chemotherapy are often associated with drug-induced liver injury (DILI). Therefore, cancer patients, as a sensitive group receiving chemotherapy, require precise evaluation of liver and renal functions to select the most appropriate chemotherapy agent and necessary medication [54]. These findings highlight the importance of finding a medicine to control hepatotoxicity and improve liver function in cancer patients. Therefore, this study was conducted to investigate the effectiveness of silymarin on liver and renal function tests and related markers in cancer patients undergoing chemotherapy in an outpatient setting. To the best of our knowledge, this clinical trial is the first human study to examine the effects of silymarin on serum levels of antioxidant markers and liver enzymes in breast cancer patients with liver damage.

The preliminary findings of this study indicated that receiving 140 mg of silymarin supplement twice daily over a 60-day period can lead to significant changes on liver enzymes such as bilirubin and ALP compared to the placebo. However, these changes were not significant for liver enzymes including ALT, AST, and BUN compared to the placebo. The multiple beneficial effects and properties of silymarin, such as its antioxidant, anti-inflammatory, liver-protective, anti-fibrotic properties, and its role in insulin resistance modulation, have been identified in many studies [54, 55]. Therefore, the findings of this study are comparable and open to further examination with the results of other studies.

Based on the findings of Kim et al., the oral consumption of silymarin may have a significant impact on liver damage caused by stress in mice, particularly antioxidant and anti-inflammatory damages [56]. Additionally, Yemişen et al. reported that silymarin had positive effects on reversing liver damage caused by burns in burned rats with both topical and systemic silymarin treatment [57]. Numerous clinical trials have been conducted on the hepatoprotective effects of silymarin in various pathological conditions in different groups. Mirzaei et al. reported that the consumption of livergol tablets containing 140 mg of silymarin three times daily for 14 days by 90 trauma patients hospitalized in the intensive care unit significantly reduced liver enzymes compared to the placebo group [58]. Furthermore, in the study by Eqbali et al., comparing the changes of silymarin consumption in a patient with acute lymphoblastic leukemia (ALL) over 5 years showed that oral silymarin intake led to a partial significant decrease in ALT, AST, GGT, and bilirubin levels, but had no effect on ALP, albumin, and cholesterol [59]. In other studies, the effects of silymarin on improving liver parameters in patients with Non-alcoholic fatty liver disease (NAFLD) [60] and inhibiting the proliferation of human breast cancer cells have been proven [56].

However, contrary to the findings of the present study, the results of the Atarodi et al.'s study, which was conducted on 56 morbidly obese patients, showed that consuming 140 mg of silymarin three times a day for 4 weeks did not show any significant difference in changes in aspartate transaminase, alkaline phosphatase, liver size, cholesterol, and triglycerides between the silymarin and placebo groups [61]. Additionally, in another randomized controlled trial on patients with acute clinical hepatitis, no discernible effect on biomarkers of the inflammatory process of liver cells, including ALT and AST, was reported [62]. These contradictory results may stem from variations in study design, dosages, patient populations, and specific conditions under treatment. Furthermore, understanding molecular mechanisms and identifying optimal dosage regimens for the effective integration of silymarin in the clinical management of cancer patients is of great importance [63]. Therefore, while silymarin has protective potential, its use should be approached with caution.

Potential mechanisms and clinical implications

silymarin, the main compound found in milk thistle, prevents various toxins from entering liver cells by promoting cell regeneration and altering the outer layer of liver cells, and possesses a unique property of protecting the liver [40, 64]. Silymarin is also considered a promising candidate for addressing liver disorders associated with inflammation and oxidative stress, as it suppresses the activation of NF-kB, which regulates the expression of pro-inflammatory genes [65]. Studies also indicate that silymarin stimulates the liver to produce more bile, aiding in liver detoxification and improving digestive system function. Despite advances in pharmacology, the use of silymarin is still considered the best therapeutic option without any specific aggressive side effects [39, 66].

Other findings of this study also demonstrated that patients undergoing silymarin therapy tolerated it well, and no side effects were observed among the participants. Only one individual reported nausea and vomiting as a result. According to the results of studies, the most common side effects of silymarin are gastrointestinal symptoms including diarrhea, dyspepsia, irregular bowel movements, and nausea [67]. Our results are in line with previous studies that have confirmed the safety of silymarin [68]. Therefore, silymarin as a complementary medicine can be beneficial in managing pathological conditions such as a wide range of cancers, alcoholic liver diseases, liver cirrhosis, Amanita mushroom poisoning, viral hepatitis, drug-induced liver diseases, and drug-induced kidney damage.

Study limitations and suggestions

Our study had limitations that need to be addressed. Firstly, patients may be influenced by incorrect conversations and recommendations from their surroundings and may refrain from taking their medication, which can be addressed through further education and continuous efforts to raise awareness. Secondly, due to limitations, the mechanism of drug action on changes in renal parameters was not investigated, which could be explored in future studies. Additionally, there was no follow-up period after the completion of the drug regimen, which could be a focus in future studies. Specific liver tumor markers associated with breast cancer, such as CA 15−3 and CEA, can provide further insights. Therefore, liver and kidney tissue biopsy samples can be utilized for hepatorenal histological studies. However, it should be noted that liver biopsies are invasive procedures that can carry significant risks, especially in patients undergoing chemotherapy. Therefore, despite the existing limitations, the present study provides preliminary evidence that silymarin may be a safe and effective supportive care agent in improving liver function in patients undergoing chemotherapy.

Conclusion

The results of this clinical trial study showed that supplementation with 140 mg of silymarin two times daily could significantly lower the serum levels of Bili and ALP in breast cancer patients with increased levels of liver enzymes. The results of this study may provide a valuable opinion on whether silymarin can be used as adjuvant therapy for the management or treatment of liver disease of cancer patients. The data presented on the efficacy and safety of silymarin may provide more foundation for further trials and for a possible use in clinical practice. Therefore, further studies with larger sample sizes and longer follow-up durations are required to better determine the efficacy of this treatment modality.

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Author contributions

SSE: Methodology, Project administration, Data curation, Software, Validation, Writing–original draft. AH: Investigation, Methodology, Writing–original draft. ShHJ: Writing–review and editing. ZA: Writing–review and editing. HA: Conceptualization, Methodology, Funding acquisition, Formal Analysis, Supervision, Visualization, Writing–original draft, Writing–review and editing.

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Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.763). Also, this study was conducted based on the approval of the clinical trial protocol (**Registration Number**: IRCT20201123049474N2, **First Trial Registration**: 16/08/2021, **Access**: https://www.irct.behdasht.gov.ir/trial/57641) and according to the CONSORT reporting guidelines. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants or their legal guardians/next of kin. The informed consent form included elements such as the introduction of the research, the procedures involved, the manner of participation, benefits and potential side effects, costs, alternative methods, confidentiality of information, the researcher's accountability to answer queries, the right to decline or withdraw from the study, and the affirmation of the consent form.

Competing interests

The authors declare no competing interests.

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