Safety and toxicity of silymarin, the major constituent of milk thistle extract: An updated review

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Milk thistle (Silybum marianum) is a medicinal plant from the Asteraceae family. Silymarin is the major constituent of milk thistle extract and is a mixture of some flavonolignans such as silybin, which is the most active component of silymarin. It is most commonly known for its hepatoprotective effect. Also, studies have shown other therapeutic effects such as anticancer, anti-Alzheimer, anti-Parkinson, and anti-diabetic, so its safety is very important. It has no major toxicity in animals. Silymarin was mutagen in Salmonella typhimurium strains in the presence of metabolic enzymes. Silybin, silydianin, and silychristin were not cytotoxic and genotoxic at concentration of 100 μM. Silymarin is safe in humans at therapeutic doses and is well tolerated even at a high dose of 700 mg three times a day for 24 weeks. Some gastrointestinal discomforts occurred like nausea and diarrhea. One clinical trial showed silymarin is safe in pregnancy, and there were no anomalies. Consequently, caution should be exercised during pregnancy, and more studies are needed especially in humans. Silymarin has low-drug interactions, and it does not have major effects on cytochromes P-450. Some studies demonstrated that the use of silymarin must be with caution when co-administered with narrow therapeutic window drugs.

KEYWORDS
adverse reactions, safety, Silybum marianum, Silymarin, toxicity

1 | INTRODUCTION

Silybum marianum belongs to the Asteraceae family and also known as milk thistle. This plant is indigenous to Southern Europe, Australia, North and South America, Northern Africa, and some parts of Asia. From ancient times until now, milk thistle has been used for treatment of liver diseases and increasing milk production in lactating mothers (Abenavoli, Capasso, Milic, & Capasso, 2010; Bazzano et al., 2016; Capasso, Aviello, & Capasso, 2009; Negi et al., 2008). It was used to protect liver against poisoning from snake bites and remove excess bile from the gallbladder (Ross, 2008). Silymarin, the major constituent of milk thistle extract (collection of flavonolignans such as silybin A and B, isosilybin A and B, silibinin, silydianin, and silychristin) is found in the seeds, leaves, and fruits of S. marianum (Karimi, Vahabzadeh, Lari, Rashedinia, & Moshiri, 2011; Luper, 1998; Napolitano et al., 2013). Silybin is the major constituent of silymarin and has the most active therapeutic effects among the other flavonolignans (Bijak, 2017; Dixit, Baboota, Kohli, Ahmad, & Ali, 2007). Oral bioavailability of silymarin is low due to little solubility in water. However, especial formulations were made that increased its solubility and absorption (Bijak, 2017).

Silymarin has various beneficial effects especially in liver diseases with its known hepatoprotective effects (Vargas-Mendoza et al., 2014). Positive roles of silymarin were showed on nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, and fibrosis in experimental human hepatocytes. Silybin interferes in oxidative stress, accumulation of fat in liver, and insulin resistance (Federico, Dallio, & Loguercio, 2017; Marin et al., 2017). It improves functional liver tests...
(Aller et al., 2015) and leads to a reduction in hepatotoxicity induced by high doses of acetaminophen and can diminish oxidative stress in mice (Brandon-Warner et al., 2012; Papackova et al., 2018). In patients with chronic hepatitis C, silymarin has antiviral (Lani et al., 2015; Polyak, Ferenci, & Pawlotsky, 2013) and hepatoprotective role (Polyak et al., 2013). At certain concentrations, milk thistle is antibacterial and showed inhibitory effect on biofilm formation (Eren & Yurtcu, 2015). Clinically, silymarin showed anti-Parkinson and anti-Alzheimer effects (Ullah & Khan, 2018; Yaghmaei, Azarfar, Dezfulian, & Ebrahimi-Habibi, 2014); in addition, anti-inflammatory effects of silymarin was significant in patients with arthritis (Hussain et al., 2009). Anticancer activity of milk thistle was observed in a variety of cancer cells (Agarwal, Agarwal, Ichikawa, Singh, & Aggarwal, 2006; Won et al., 2018). In mice with breast cancer, silymarin had anticancer activity and reduced tumor volume, consequently inhibited tumor growth. It has also diminished toxicity of chemotherapy agents. Furthermore, silymarin prevents hand-foot syndrome induced by capecitabin (Elyasi, Shojae, Allahyari, & Karimi, 2017; Forghani, Khorramizadeh, & Waller, 2014). Topical formulations of silymarin suppressed skin tumor and protected the skin against oxidative stress caused by UV radiation in mice. It has protective effect against radiodermatitis in patients with breast cancer (Karbasforooshan, Hossein, Elyasi, Fani Pakdel, & Karimi, 2018; Katiyar, Meleth, & Sharma, 2008). Topical silymarin was useful in the treatment of atopic dermatitis. Moreover, it showed a wound-healing effect (Mady, Hanaa Essa, El-Ammawi, Abdelkader, & Hussein, 2016; Sharifi et al., 2012). Milk thistle extract has immune system modulatory effect. It was useful for treatment of inflammation in peritoneal dialysis patients due to its immunomodulatory effect (Balouchi, Gharagholooh, Esmaeil, Mirmoghaddasi, & Moayedi, 2014; Karimi, Hassanzadeh-Josan, Memar, Esmaeili, & Riahi-Zanjani, 2018; Nazemian et al., 2010). This phytotherapy is useful in the treatment of metabolic syndrome (Tajmohammadi, Razavi, & Hosseinzadeh, 2018), and this effect can be improved by coadministration of silymarin with berberin (Fogacci, Grassi, Rizzo, & Cicero, 2019). In diabetic patients, silymarin has useful effect in reduction of post prandial plasma glucose, HbA (1c), and fasting blood glucose (Hussain, 2007; Voroneanu, Nistor, Dumea, & Apetri, 2016) as well as it showed preventive effect against progression of diabetic complications such as diabetic nephropathy (Khazim, Gorin, Cavaglieri, Abboud, & Fanti, 2013; Rafieian-Kopaie & Nasri, 2012; Stolf, Cardoso, & Acco, 2017).

Due to the extensive use and therapeutic potential of this plant in humans and especially the therapeutic role of silymarin in liver diseases, this article discusses the safety, toxicity, and adverse reactions of milk thistle and silymarin (Figure 1, Table 1).

1.1 Literature search

We utilized Web of Science and PubMed databases for evaluation of adverse events and safety of silymarin. Only articles in English were used. We collected human studies that were done on healthy and patient volunteers and silymarin (standardized extract) administered orally, intravenously, or topically. Human studies are from the beginning of 2007 until the end of 2018, because an article was published by Tamayo and Diamond (2007) that discussed the safety and adverse reactions of milk thistle in humans. In addition, we reviewed human studies before 2007, which did not exist in the previous articles. Animal toxicity, cytotoxicity in normal cell culture, mutagenicity, genotoxicity, and also safety of silymarin during pregnancy in humans and animals were included in this manuscript. Search terms and keywords included S. marianum, milk thistle, silymarin, safety, adverse

![FIGURE 1](wileyonlinelibrary.com)
<table>
<thead>
<tr>
<th>Healthy/patient</th>
<th>Route of administration</th>
<th>Dose of administration</th>
<th>Duration of administration</th>
<th>Adverse reactions and toxicity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>Oral</td>
<td>140 mg three times daily</td>
<td>28 days</td>
<td>No adverse effect</td>
<td>Zhu et al., 2013</td>
</tr>
<tr>
<td>Healthy</td>
<td>Oral</td>
<td>420 mg daily</td>
<td>63 days</td>
<td>No toxicity</td>
<td>Di Pierro et al., 2008</td>
</tr>
<tr>
<td>Healthy</td>
<td>Oral</td>
<td>400 mg/day</td>
<td>10 days</td>
<td>No adverse effect and toxicity</td>
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<td>Patients with hepatotoxicity induced by Amotoxin</td>
<td>Intravenous silibinin</td>
<td>5 mg/kg on first day then 20 mg/kg over 24 hr</td>
<td>24 hr</td>
<td>Safe and tolerated well, but had mild flushing</td>
<td>Mengs et al., 2012</td>
</tr>
<tr>
<td>Patients with non-cirrhotic HCV</td>
<td>Oral</td>
<td>140, 280, 560 and 700 mg three times daily</td>
<td>7 days</td>
<td>No adverse reactions, but nausea and headache were observed at 280 mg</td>
<td>Hawke et al., 2010</td>
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<td>Patients with hepatitis C</td>
<td>Oral</td>
<td>supplement (vitamin E, phospholipid, and 94-mg silybin)</td>
<td>12 months</td>
<td>No major adverse events but weight loss, irritability, hyperglycemia, muscle pain, and hypercholesterolemia were reported</td>
<td>Malaguarnera et al., 2016</td>
</tr>
<tr>
<td>Patients with hepatitis C</td>
<td>Intravenous</td>
<td>20 mg/kg/day</td>
<td>14 or 21 days</td>
<td>No major toxicity, but heat sensation and gastrointestinal symptoms were reported</td>
<td>Rutter et al., 2011</td>
</tr>
<tr>
<td>Patients with cirrhosis induced by diabetes</td>
<td>Oral</td>
<td>600 mg/day</td>
<td>12 months</td>
<td>No side effect</td>
<td>Velussi et al., 1997</td>
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<td>Patients with nonalcoholic fatty liver disease and hepatitis C</td>
<td>Oral</td>
<td>280 or 560 mg three times daily</td>
<td>7 days</td>
<td>Mild to moderate adverse effects like gastrointestinal and neurological events</td>
<td>Schriever et al., 2011</td>
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<td>Patients with hepatitis C</td>
<td>Infusion</td>
<td>1,400 mg/day</td>
<td>2 days</td>
<td>Tolerated well, but abdominal pain, vomiting and diarrhea, and heat sensation were observed</td>
<td>Biermer et al., 2012</td>
</tr>
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<td>Patients with nonalcoholic fatty liver disease</td>
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<td>140 mg twice daily</td>
<td>12 weeks</td>
<td>No toxicity</td>
<td>Zhong et al., 2017</td>
</tr>
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<td>Patients with acute hepatitis</td>
<td>Oral</td>
<td>140 mg three times daily</td>
<td>4 weeks</td>
<td>No adverse effects</td>
<td>El-Kamary et al., 2009</td>
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<td>Patients with cirrhosis</td>
<td>Oral</td>
<td>140 mg three times daily</td>
<td>41 months</td>
<td>No adverse effects</td>
<td>Ferenci et al., 1989</td>
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<td>Patients with nonalcoholic fatty liver disease</td>
<td>Oral</td>
<td>94-mg silybin two times daily</td>
<td>12 months</td>
<td>Mild diarrhea, pruritus, and dysgeusia</td>
<td>Loguercio et al., 2012</td>
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<tr>
<td>Patients with allergic rhinitis</td>
<td>Oral</td>
<td>140 mg three times daily</td>
<td>1 month</td>
<td>No toxicity and adverse effects</td>
<td>Bakhshaei et al., 2011</td>
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<td>Patients with tuberculosis</td>
<td>Oral</td>
<td>140 mg three times daily</td>
<td>4 weeks</td>
<td>No adverse effects</td>
<td>Luangchosiri et al., 2015</td>
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<td>Patients with chronic hepatitis C</td>
<td>Oral</td>
<td>420 and 700 mg three times daily</td>
<td>24 weeks</td>
<td>Well tolerated</td>
<td>Fried et al., 2012</td>
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<tr>
<td>Patients with tuberculosis</td>
<td>Oral</td>
<td>140 mg three times daily</td>
<td>2 weeks</td>
<td>Well tolerated, without adverse effects</td>
<td>Marjani et al., 2016</td>
</tr>
<tr>
<td>Healthy/patient</td>
<td>Route of administration</td>
<td>Dose of administration</td>
<td>Duration of administration</td>
<td>Adverse reactions and toxicity</td>
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<tr>
<td>Patients with HIV</td>
<td>Oral</td>
<td>150 mg three times daily</td>
<td>2 weeks</td>
<td>Well tolerated</td>
<td>Moltó et al., 2012</td>
</tr>
<tr>
<td>Patients with cancer that receiving Cisplatin</td>
<td>Oral</td>
<td>140 mg two times daily</td>
<td>7 days</td>
<td>No adverse effects</td>
<td>Momeni et al., 2015</td>
</tr>
<tr>
<td>Patients with cancer that receiving Cisplatin</td>
<td>Oral</td>
<td>420 mg/day</td>
<td>21 days</td>
<td>No adverse effects</td>
<td>Shahbazi et al., 2015</td>
</tr>
<tr>
<td>Patients with prostate cancer</td>
<td>Oral</td>
<td>2.5, 5, 10, 15, and 20-mg SiliPhos three times daily</td>
<td>1 month</td>
<td>Gastrointestinal effect and hyperbilirubinemia and also mild increasing in creatin, calcium, and halitosis</td>
<td>Flaig et al., 2007</td>
</tr>
<tr>
<td>Patients with neck and head cancer</td>
<td>Oral</td>
<td>420 mg/day</td>
<td>6 weeks</td>
<td>No adverse effect</td>
<td>Elyasi et al., 2016</td>
</tr>
<tr>
<td>Patients with colitis</td>
<td>Oral</td>
<td>140 mg/day</td>
<td>6 months</td>
<td>No major toxicity but abdominal pain, headache, and nausea were prevalent</td>
<td>Rastegarpanah et al., 2015</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>Oral</td>
<td>140 mg three times daily</td>
<td>3 months</td>
<td>Headache, vomiting, and nausea</td>
<td>Fallahzadeh et al., 2012</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>Oral</td>
<td>Berberol (105-mg milk thistle) two times daily</td>
<td>12 months</td>
<td>No toxicity, but asthenia and headache were observed</td>
<td>Di Pierro et al., 2015</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>Oral</td>
<td>210-mg silymarin + 1,000-mg berberin daily</td>
<td>120 days</td>
<td>Mild abdominal pain without serious adverse effects</td>
<td>Di Pierro et al., 2013</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>Oral</td>
<td>140 mg three times daily</td>
<td>45 days</td>
<td>No side effects</td>
<td>Ebrahimpour Koujan et al., 2015</td>
</tr>
<tr>
<td>Patients with arthitis</td>
<td>Oral</td>
<td>300 mg/day</td>
<td>8 weeks</td>
<td>Reduction in interleukins</td>
<td>Hussain et al., 2009</td>
</tr>
<tr>
<td>Patients with hepatic toxicity and acute lymphoblastic leukemia</td>
<td>Oral</td>
<td>5.1 mg/kg/day of silybinin</td>
<td>28 days</td>
<td>No unexpected toxicity</td>
<td>Ladas et al., 2010</td>
</tr>
<tr>
<td>Patients with beta thalassemia</td>
<td>Oral</td>
<td>140 mg three times daily</td>
<td>6 months</td>
<td>No toxicity and well tolerated</td>
<td>Hagag et al., 2015</td>
</tr>
<tr>
<td>Patients with beta thalassemia major</td>
<td>Oral</td>
<td>140 mg three times daily</td>
<td>9 months</td>
<td>No serious adverse effects, just three patients had bloating and dyspepsia</td>
<td>Moayedi et al., 2013</td>
</tr>
<tr>
<td>Patients with beta thalassemia</td>
<td>Oral</td>
<td>140 mg three times daily</td>
<td>14 days</td>
<td>No major toxicity</td>
<td>Kawaguchi-Suzuki et al., 2014</td>
</tr>
<tr>
<td>Patients with beta thalassemia</td>
<td>Oral</td>
<td>420 mg/day</td>
<td>9 months</td>
<td>No adverse effects</td>
<td>Darvishi Khezri et al., 2016</td>
</tr>
<tr>
<td>Pregnant women with chronic hepatitis B</td>
<td>Oral</td>
<td>150 mg two times daily</td>
<td>13 weeks</td>
<td>No toxicity and anomalies</td>
<td>Hung et al., 2008</td>
</tr>
<tr>
<td>Women with preeclampsia</td>
<td>Oral</td>
<td>70 mg</td>
<td>3 and 24 hr after pregnancy</td>
<td>Adverse effects were not reported</td>
<td>Baghbahadorani &amp; Miraj, 2017</td>
</tr>
<tr>
<td>Patients with melasma</td>
<td>Topical</td>
<td>0.1 and 0.2% two times daily</td>
<td>4 weeks</td>
<td>No side effect</td>
<td>Sarkar et al., 2014</td>
</tr>
<tr>
<td>Patients with gastrointestinal cancer</td>
<td>Topical</td>
<td>Gel 1% two times per day</td>
<td>9 weeks</td>
<td>No adverse effects</td>
<td>Elyasi et al., 2017</td>
</tr>
</tbody>
</table>
reaction, toxicity, cytotoxicity, genotoxicity, mutagenicity, reproductive toxicity, human clinical trial, and drug interaction.

2 | SAFETY AND TOXICITY OF SILYMARIN IN ANIMALS

According to an article published by the U.S. Department of Health and Human Services in the National Toxicology Program, male and female mice and rats were treated with silymarin and followed up for 3 months and 2 years. In the 3-months study on rats, silymarin was administered orally at the concentrations of 0, 3,125, 6,250, 12,500, 25,000, and 50,000 ppm (equivalent to 260, 525, 1,050, 2,180, and 4,500 mg silymarin/kg body weight for male rats and 260, 510, 1,050, 2,150, and 4,550 mg/kg for female rats), and in the 2-years study, silymarin was administered at concentrations of 0, 12,500, 25,000, or 50,000 ppm (equivalent to 570, 1,180, and 2,335 mg/kg for male rats and 7,770 mg/kg for male mice and 1,500, 3,175, and 7,180 mg/kg for female mice), and in the 2-years study, the animals received silymarin at concentrations of 0, 3,125, 6,250, 12,500, 25,000, or 50,000 ppm through their diets. Weights of reproductive organs and sperm quality criteria such as sperm motility were diminished 5%, 11%, and 9% at concentrations of 12,500, 25,000, and 50,000 ppm, respectively, in the 2-years study on rats, there were no significant changes in mean body weights, and no major toxicity was occurred.

In the 3-months study on mice, animals received silymarin at concentrations of 0, 3,125, 6,250, 12,500, 25,000, or 50,000 ppm (equivalent to 640, 1,340, 2,500, 5,280, and 11,620 mg/kg for male mice and 580, 1,180, 2,335, 4,800, and 9,680 mg/kg for female mice), and in the 2-years study, they received silymarin at concentrations of 0, 12,500, 25,000, or 50,000 ppm (equivalent to 1,610, 3,530, and 7,770 mg/kg for male mice and 1,500, 3,175, and 7,180 mg/kg for female mice). In the 3-months study, mean body weights and sperm quality did not change significantly, and there was no major toxicity. However, thymus weights were reduced at the concentrations of 25,000 and 50,000 ppm compared with the control group. In the 2-years study, no death was occurred, and there was no major toxicity, but mean body weights were reduced in the 25,000 and 50,000-ppm concentrations compared with the control group (Dunnick et al., 2011).

2.1 | Teratogenicity and reproductive toxicity of silymarin in animals

Female mice received silymarin orally at doses of 50, 100, and 200 mg/kg/day during their pregnancy. At the end of the study, silymarin showed teratogenic effects, and fetal weights were lower than the control group. Anomalies were observed in the face, vertebrae, and skull (Gholami et al., 2016). More studies must be done on silymarin teratogenicity because there is still little information in pregnant animals.

In 3-months study on mice and rats, the animals received oral silymarin at the concentrations of 0, 3,125, 6,250, 12,500, 25,000, or 50,000 ppm through their diets. Weights of reproductive organs and sperm quality in male and female mice did not change compared with control. However, sperm quality in rats decreased (Dunnick et al., 2011). However, more studies are needed about reproductive toxicity in humans and animal models.

3 | MUTAGENICITY, GENOTOXICITY, AND CYTOTOXICITY OF SILYMARIN

For evaluation of mutagenicity of milk thistle extract, silymarin was tested on some Salmonella typhimurium strains and one Escherichia coli strain in the presence and absence of activation enzymes. Silymarin was mutagenic in S. typhimurium strains TA100 and TA98 in the culture media containing the enzymes, but silybin did not show mutagenicity in all strains that were tested. Silymarin did not have chromosomal aberration, and replication of micronucleated nonchromatic erythrocytes did not change in mice-received silymarin within 3 months (Dunnick et al., 2011). In another study, silybin, silydianin, and silychristin at concentrations up to 100 μM were safe and did not show genotoxicity and cytotoxicity on blood platelets (Bijak, Synowiec, Sitarek, Sliwiński, & Saluk-Bijak, 2017). Oral ingestion
of silymarin did not have chromosomal aberration in bone marrow cells in mice-received silymarin at the doses of 2, 4, and 20-mg/kg body weight. In this study, combination of cyclophosphamid with silymarin were positive control and deionized water was negative control (Anwar, Madkor, Ahmed, & Wagih, 2018).

4 | SAFETY AND ADVERSE REACTIONS OF ORAL SILYMARIN IN HUMANS

In this section, we discussed safety and adverse reactions of silymarin in humans. The clinical trials that we assessed were done on healthy volunteers and patients with various illnesses. In each section, silymarin was administered at different doses, periods, and routes of administration. Totally, silymarin was safe at therapeutic doses in human, and only transient side effects like gastrointestinal upsets were seen in some studies. In the following, we discussed more details about the adverse reactions and toxicity of silymarin in humans (Table 1).

4.1 | Healthy people

One clinical trial in male and female healthy volunteers showed no adverse reaction after oral administration of standardized silymarin at the dose of 140 mg three times daily for 28 days (Zhu et al., 2013). Another research was done on 50 healthy women during lactation. In this trial, 420 mg/day of micronized silymarin administered for 63 days by oral route. It did not demonstrate toxic effects, and tolerance was very good (Di Pierro, Callegari, Carotenuto, & Tapia, 2008). There were no adverse reactions in 22 normal healthy volunteers who received 400-mg silymarin and 295-mg L-arginine for 10 days. The results of experiments on blood and urine collected in Days 0, 10, and 27 indicated that silymarin did not have toxicity (Valentová et al., 2013). In another trial on healthy people, oral intake of capsules containing 175 mg of milk thistle extract or 140-mg silymarin three times a day for 14 days had no major toxicity, and no adverse reactions were observed (Kawaguchi-Suzuki et al., 2014).

4.2 | Patients with liver diseases

4.2.1 | Hepatitis C

One study was done on 24 male and female patients infected with hepatitis C virus (HCV) that their hepatitis was non-cirrhotic and failed with interferon treatment. Patients received oral silymarin at the doses of 140, 280, 560, 700 mg three times daily for 7 days. Nausea and headache were observed at the dose of 280 mg. However, no adverse effects related to the drug were reported (Hawke et al., 2010). In another clinical study on these patients, they received PEGylated-interferon alfa 2b and ribavirin and one supplement daily (contains 94-mg silybin, vitamin E, and phospholipids) for 12 months. In this trial, no intense adverse effects were reported, although some symptoms such as weight loss, muscle pain, irritability, hyperglycemia, joint pain, and hypercholesterolemia were observed (Malaguarnera et al., 2016). As well as in another trial on these patients, 27 male and female patients (who were treated with ribavirin and interferon and still hepatitis C virus ribonucleic acids were detectable) received 20 mg/kg of intravenous silymarin for 14 or 21 days. Their blood was collected at Days 1, 8, 15, and 22 and every 4 weeks. This study demonstrated that silymarin did not have major toxicity, although 12 patients felt heat sensation, and 15 patients had gastrointestinal symptoms during treatment. Slight increase in bilirubin (0.98 ± 0.35 to 2.12 ± 0.99 mg/dl) was observed in all patients in this trial (Rutter et al., 2011). Moreover, oral ingestion of 630 mg/day of silymarin for 24 weeks was safe in these patients (male and female; Kalantari, Shahshahan, Hejazi, Ghaefghazi, & Sebghatolah, 2011). Intravenous administration of silymarin to patients with hepatitis C (1,400-mg/day silymarin over 120–360 min) for 2 days during treatment with PEGylated-interferon alpha-2a was tolerated well; however, some moderate adverse reactions such as abdominal pain, vomiting, diarrhea, and heat sensation were reported. Patients did not have these complications for more than 2 days (Biermer et al., 2012). In another trial, oral consumption of 420 and 700-mg silymarin three times daily for 24 weeks was safe in these patients. As a result, it can be concluded that high dose of silymarin is well tolerated in patients with hepatitis C (Fried et al., 2012).

4.2.2 | Nonalcoholic fatty liver disease

In a meta-analysis article (studied on patients with nonalcoholic fatty liver disease), intake of 140-mg silymarin two times a day for 12 weeks was considered safe, and no adverse effects and toxicities were reported (Zhong et al., 2017). In patients with acute hepatitis, treatment with 140-mg silymarin three times daily for 4 weeks was tolerated well, and no adverse event was noted. In this clinical study, the patients were followed up for an additional 4 weeks after treatment with silymarin (El-Kamary et al., 2009). There were no severe adverse events in nonalcoholic fatty liver disease who received 94-mg silybin and 194-mg phosphatidylcholine formulated with 89.28-mg vitamin E two times a day for 12 months. Although, some transient side effects like diarrhea, pruritus, and dysgeusia were observed (Loguercio et al., 2012).

4.2.3 | Other liver diseases

In a clinical study, there were no severe adverse effects in patients with acute hepatotoxicity induced by Amatoxin poisoning who received intravenous single dose of sterile lyophilisate silibinin at the dose of 5 mg/kg in the first day and continued at the dose of 20 mg/kg over 24 hr; however, mild degree of flushing appeared, and silibinin was well tolerated (Mengs, Pohl, & Mitchell, 2012). Patients with cirrhosis induced by diabetes mellitus received 600-mg oral silymarin and did not show any adverse reactions. Duration of this study was 12 months (Velussi et al., 1997). In 40 male and female patients with nonalcoholic fatty liver disease and hepatitis C, oral silymarin was administered at the dose of 280 or 560 mg three times
daily for 7 days. Gastrointestinal and neurological events were observed at the dose of 280 mg. In addition, abdominal pain and upper respiratory infection in the 560-mg silymarin group were reported, though the adverse events were mild to moderate (Schriever et al., 2011).

4.3 | Allergic rhinitis

Oral consumption of 140-mg silymarin three times a day for 1 month showed beneficial effects on symptoms of rhinitis in 94 patients with allergic rhinitis and a positive skin prick test. It was safe, and no major adverse reactions were observed. The goal of this trial was the assessment of silymarin role in allergic rhinitis symptoms due to its antioxidant effect (Bakhshae et al., 2011).

4.4 | Tuberculosis

In patients with tuberculosis, one tablet of silymarin (140 mg) was given every 8 hr to patients who had received antituberculosis drugs. At Weeks 2 and 4 after the beginning of the study, no significant adverse effects of silymarin were observed. In another trial, there was not any adverse reactions with this dose of silymarin for 8 weeks (Luangchosiri et al., 2015). Also, oral consumption of 140-mg silymarin twice daily for 8 weeks was safe, and no adverse reactions were reported (Heo et al., 2017). In a double-blind clinical study on patients with tuberculosis, oral intake of 140-mg silymarin three times daily for 2 weeks did not show any intense adverse effects. Some gastrointestinal upsets like nausea and anorexia were occurred (Marjani et al., 2016).

4.5 | Immune deficiency virus (HIV)

For evaluation of silymarin effect on the pharmacokinetics of darunavir–ritonavir in HIV-infected patients, 150-mg silymarin was administered three times a day for 2 weeks. In this trial, 15 males were under treatment with darunavir–ritonavir at the doses of 600 and 100 mg twice a day. Silymarin tolerated well and was safe in combination with darunavir and ritonavir (Moltó et al., 2012).

4.6 | Cancer

There were no adverse reactions in oral administration of 140-mg silymarin two times a day before taking cisplatin for 7 days in 60 patients with malignancy (Momeni, Hajigholami, Geshnizjani, & Soleiman, 2015). In another study on patients who received cisplatin, 420-mg/day silymarin was administered orally 24–48 hr before cisplatin infusion and continued for 21 days. No adverse reactions were reported for silymarin (Shahbazi et al., 2015). In another study, patients with prostate cancer received 2.5, 5, 10, 15, and 20 mg of oral silybin-phytosome (siliphos) three times daily for 1 month. Some adverse reactions like gastrointestinal effects and hyperbilirubinemia were reported and also a few mild adverse effects such as increase in creatinine, calcium, and halitosis were reported (Flaig et al., 2007).

In a double-blind clinical trial, patients with neck and head cancer who had undergone radiotherapy received silymarin tablets (420 mg/day) for 6 weeks. This study was done for evaluation of silymarin effects to reduce severity of mucositis induced by radiotherapy and its occurrence. In this trial, silymarin was tolerated well, and it had no adverse effects (Elyasi, Hosseini, Niazi Moghadam, Aledavood, & Karimi, 2016). In another double-blind, placebo controlled clinical trial, patients with a prostate cancer history received silymarin in combination with selenium 2–3 months after prostatectomy. The dose of silymarin was 570 mg daily, and duration of study was 6 months. No adverse reactions were reported for silymarin, and it was effective in preventing prostate cancer progression when co-administered with selenium (Vidlar et al., 2010). Patients with colorectal cancer received 188-mg silybin, 288-mg phosphatidylcholine, and 60-mg vitamin E daily in combination with regorafenib. The date of the study was from November 2013 to March 2017. No adverse reactions were reported for silybin in this trial, and none of patients discontinued the treatment due to side effects (Belli et al., 2017).

4.7 | Ulcerative colitis

For assessment of positive effect of silymarin on patients with ulcerative colitis, a randomized, double-blinded clinical trial was done on these patients. They received silymarin during their standard treatment, and the dose of silymarin was 140 mg/day orally within 6 months. Diarrhea, abdominal pain, headache, and nausea were the most prevalent adverse reactions of silymarin. However, these adverse reactions were transient, and silymarin did not have any major toxicity (Rastegarpanah et al., 2015).

4.8 | Diabetes

In a randomized double-blinded clinical trial, 140-mg silymarin three times daily in combination with renin-angiotensin system inhibitors were given to diabetic type 2 patients for 3 months. After this research, one patient died because of myocardial infarction, though she had previous heart disease. Other adverse effects of silymarin were headache, vomiting, and nausea (Fallahzadeh et al., 2012). In another study on 45 diabetic and hypercholesterolemic patients, they received Berberol® tablets containing 588-mg Berberis aristata extract and 105-mg milk thistle extract two times per day for 12 months. Berberol® did not have toxicity and well tolerated, but asthenia and headache were observed. In addition, two from 15 patients in Berberol® plus statins group had cramps, and one patient reported headache and constipation for a few days (Di Pierro, Bellone, Rapacioli, & Putignano, 2015). In another trial, patients with diabetes type 2 received total dose of 1,000-mg berberin and 210-mg silymarin per day for 120 days. In this trial, mild abdominal discomfort was seen in 15% of the patients, though it was transient, and generally anyone had serious adverse effects (Di Pierro et al., 2013). There were no side
effects or any symptoms in diabetic patients who received 140-mg dried extract of *S. marianum* orally every 8 hr for 45 days (Ebrahimpour Koujan, Gargari, Mobasser, Valizadeh, & Asghari-Jafarabadi, 2015).

4.9 | Arthritis

For assessment of anti-inflammatory effect of silymarin on patients with knee osteoarthritis, silymarin was administered at the dose of 300 mg/day orally for 8 weeks. Silymarin was studied in comparison with nonsteroidal anti-inflammatory drugs in 220 patients (79 males and 141 females). Consequently, reduction in the levels of elevated interleukins were observed, and silymarin tolerance was good for the patients, and no toxicity was observed (Hussain, Jassim, Numan, Al-Khalifa, & Abdullah, 2009). In a double-blind clinical study, 30 males and 30 females with arthritis rheumatoid treated with methotrexate (12 mg/week) and silibinin (120 mg two times in a day) for 3 months. No toxicity and adverse reaction were reported for silibinin in this trial (Hussain, Mortada, Jasim, & Gorial, 2016).

4.10 | Preeclampsia

In a randomized clinical trial, 60 patients with preeclampsia received 70-mg silymarin orally after their pregnancy (3 and 24 hr after termination of pregnancy). The purpose of this study was evaluation of the effect of silymarin on preeclampsia and hepatic injury induced by high blood pressure. Aspartate aminotransferase and alanine aminotransferase diminished (36 and 60 hr after the end of pregnancy), and no adverse reactions were reported in this research (Baghbahadorani & Miraj, 2017).

4.11 | Blood diseases

In children with hepatic toxicity and acute lymphoblastic leukemia, the oral intake of milk thistle capsules did not show toxicity. Intensity and occurrence of side effects were the same as the control group. Each capsule contained standard silibinin (therapeutic dose was 5.1 mg/kg/day of silibinin) for 28 days (Ladas et al., 2010). In one research on patients with beta thalassemia, oral administration of 140-mg silymarin three times daily for 6 months in combination with deferiprone (20-40 mg/kg/day) was without any toxicity. Silymarin also showed iron-chelating activity, and after the termination of treatment, the level of ferritin and iron were diminished, but no significant changes were observed in serum creatinine, alanine aminotransferase, and aspartate aminotransferase (Hagag, Elfarag, Elrifaey, & Abd El-Lateef, 2015). In another study on patients, they treated with subcutaneous desferrioxamine and oral 140-mg silymarin three times in a day for 9 months. In this study, just three patients had bloating and dyspepsia. Although, these symptoms were resolved after 4 weeks, and silymarin was tolerated well with no serious adverse reactions (Moayedi et al., 2013). For evaluation of silymarin effect on serum levels of interleukins in patients with Beta thalassemia, silymarin administered 420 mg/day for 6 months, and no major adverse reactions were observed in this trial (Balouchi et al., 2014). In one review article, patients with beta thalassemia received silymarin (420 mg/day) and desferrioxamine for 9 months to reduce iron and serum ferritin levels. In this study, silymarin was safe, and no adverse reactions occurred (Darvishi Khezri et al., 2016). For evaluation of iron-chelating effect of silybin, patients with hereditary haemochromatosis ingested 140-mg silybin (Legalon® Forte) daily for 12 weeks. This trial showed that silybin has iron-chelating activity, and no toxicity was occurred in this trial, and it was useful in treatment of hereditary haemochromatosis (Hutchinson, Bomford, & Geissler, 2010).

5 | PREGNANCY

In one clinical study, a woman with chronic hepatitis B received lamivudine before and during her pregnancy and then received oral 150-mg silymarin two times in a day. At the 13th week of pregnancy, adverse effects were not observed, and no anomalies were seen in the fetus. Silymarin and lamivudine were safe at certain doses in pregnancy (Hung et al., 2008). However, there are still few studies about silymarin safety in human pregnancy, and more studies are needed.

6 | SAFETY AND ADVERSE EFFECTS OF TOPICAL SILYMARIN IN HUMAN

Patients with melisma were treated with topical silymarin cream 0.1% and 0.2%, two times per day for 4 weeks, and no adverse effects were reported (Sarkar, Arora, Garg, Sonthalia, & Gokhale, 2014). In a randomized, double-blinded placebo controlled trial on patients with gastrointestinal cancer who had hand-foot syndrome due to capecitabine, application of silymarin gel 1% twice daily for 9 weeks had no adverse effects (Elyasi et al., 2017). In another study on topical form of silymarin, use of silymarin 2 hr before radiation therapy for 5.5 weeks in patients with breast cancer did not have any adverse reactions, and it was effective in prevention of radiation therapy-induced dermatitis in these patients (Becker-Schiebe, Mengs, Schaefer, Bulitta, & Hoffmann, 2011).

7 | SILYMARIN EFFECT ON HUMAN CYTOCHROME P-450 AND DRUG INTERACTIONS

Oral bioavailable formulation of silymarin at therapeutic doses did not have significant inhibitory or stimulant effects on CYP1A2, CYP2C9, CYP2D6, and CYP3A4 (Beckmann-Knopp et al., 2000). It did not have significant effect on the metabolism of any drug (Leber & Knauff, 1976). However, in other studies silybin A, silybin B, and silibinin, which are constituents of silymarin, had inhibitory effect on CYP2C9 and CYP3A4. Some of these cytochromes such as CYP2C9 has effective role in warfarin metabolism (Brantley, Oberlies, Kroll, & Paine, 2010). As a result, silymarin did not have major effect on drug metabolisms although use of some drugs such as warfarin should be with caution.
8 | DISCUSSION

In this review, we collected human and animal studies. Moreover, this article discussed mutagenicity, genotoxicity, and cytotoxicity of silymarin. In most studies, silymarin was standardized based on silybin, but some studies used silibinin. This review has some limitations. In most human trials, silymarin was co-administered with another drug to improve the treatment outcome or reduce the side effects of the main drug. Therefore, adverse events of the main drug may hide the adverse events of silymarin. In animal studies, there were not many articles discussing toxicity of silymarin directly, and most studies co-administered silymarin with other chemical substances or drugs. Consequently, in animal studies, we only used articles discussing toxicity of silymarin directly. In one study during human pregnancy, it was safe. However, in one animal study, it was teratogenic. Though, more studies are needed in pregnancy in both human and animals. Consequently, ingestion of silymarin during human pregnancy should be with caution. Another important issue is silymarin formulations. Silymarin has low oral bioavailability, though this can be increased with special modifications. Most studies did not discuss absorption and formulation of silymarin. Another important issue is standardization of silymarin, and U.S. Food and Drug Administration has not approved standardization of silymarin until now. Milk thistle extract contains several flavonolignans such as silybin, silibinin, silydianin, and silychristin. It is better to investigate the toxicity and safety of these substances separately, especially silybin, which is the major constituent of silymarin, and most of the medicinal effects of sylimarin are due to the presence of this substance.

9 | CONCLUSION

Totally, it can be concluded that milk thistle is safe for humans at therapeutic doses and has few adverse reactions such as some gastrointestinal upsets. However, more trials in pregnancy are needed. It has low-drug interactions, but it must be used with caution during coadministration with drugs with a narrow therapeutic window.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this article.

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