# A Review on Pharmacological, Cultivation and Biotechnology Aspects of Milk Thistle (*Silybum marianum* (L.) Gaertn.)

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## Abstract

**Milk thistle (*Silybum marianum* (L.) Gaertn.) is one of the valuable medicinal plants which used in the treatment of liver disorders. The major active constituents in this plant are flavonolignans, collectively known as silymarin which is a mixture of three isomer silybin, silydianin and silycristin. Its therapeutic properties are due to the presence of silymarin. The seeds contain the highest amount of silymarin, but the other plant parts have less amount of this compound. The silymarin content in fruits depends on milk thistle variety and geographic and climatic condition. In this review, we summarized the accomplished investigations on aspects of medicinal, cultivation, biology and biotechnology of milk thistle.**

**Keywords:** ***Silybum marianum*, Silymarin, Silybin, Flavonolignan, Cultivation and Medicinal properties**



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# Introduction

Milk thistle (*Silybum marianum* (L.) Gaetrn) has been used since the time of ancient to treat a range of liver and gallbladder disorders (hepatitis, cirrhosis and jaundice) and to protect liver damage due to alcoholism, pharmaceutical drugs, and chemical pollutants [1, 2, 3]. Historically, milk thistle was grown in Europe as a food source. The roots can be eaten (soaked overnight to remove the bitterness); flower receptacle eaten like artichokes; the leaves eaten as a spinach substitute; the stalks eaten like asparagus [4, 5] and roasted fruits eaten as a coffee substitute [1, 4] or mixed with sea salt for use as a condiment [2, 4]. In parts of England and Scotland, the leaves were used extensively as food for cattle and horses. In some places, it cultivated as a garden ornamental [6] on rocky or sandy soils [7].

The ancient documents indicated that milk thistle was used in the Mediterranean area about 2000 years ago [1, 3]. Ancient Greek and Roman physician and herbalists were among the earliest people to use and write about milk thistle [3, 8]. Theophrastus called it under the name of “Pternix”, Pliny the Elder called it sillybum and expressed that the juice of this plant mixed with honey was desirable for “carrying off bile’’ and Dioscorides called it “Sillybon”. Historical references are particularly abundant in herbals of the middle ages [1, 3] including commendation of John Gerard (1545-1612) for expelling melancholy (depression, black bile), usage of roots, herbs and leaves of this plant for swelling and erysipelas [3, 7, 9]. By the 19$^{th}$ century, American Eclectic physicians used milk thistle for varicose veins and liver, spleen and kidney disorders [2] and in the mid-19$^{th}$ century, use of the fruit for treatment of liver diseases was revitalized by the German physician Rademacher [1, 7, 9, 10].

The biological and pharmacological properties of milk thistle are attributed to a flavanolignan complex, silymarin, which was first isolated from the fruits (achenes), (sometimes mistakenly called seeds) in 1968 [7, 10, 11, 12]. The silymarin mixture is predominantly composed of silybin (also called silibinin) [13] (30–50 %) with varying percentages of isosilybin, silychristin and silydianin [1, 2, 3, 14, 15]. Apart from silymarin and other flavonolignans, 20 – 30% of the fruit is composed of fatty acids; 25 – 30% protein; 0.038% tocopherol; 0.63% sterol and some compounds such as 3-deoxyflavanolignans mucilage [1, 2, 15, 16, 17, 18].

## Name of the Herb

### Common Names

Milk thistle is the most well-known English common name for this species and other names including Holy thistle (not to be confused with blessed thistle, *Cnicus benedictus*) [2], Mary thistle, St. Mary’s thistle, Marian thistle, Lady’s thistle, Christ’s crown, Venus thistle, Heal thistle, Variegated thistle, Pig leaves, Royal thistle, Snake milk, Sow thistle and Wild artichoke [1, 3, 7]. In different parts of the world, the plant is known by various regional names such as:

**Persian:** Mary thiqal [19], Khar mariam [20, 21]

**Arabic:** Akub, Shawk ed diman, Shawk en nassara and Hharshaf barri [22, 23]

**French:** Chardon-Marie, Chardon argente, Artichaut sauvage [22]

**Germany:** Mariendistel [1, 22]





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**Chinese:** Shui Fei Ji [5]
**Spanish:** Cardo mariano and Cardo lechero [7]

## Botanical name

*Silybum marianum* (L.) Gaertn (Syn. *Carduus marianum* L.)

*Silybum* is the name Dioscorides gave to edible thistle and *marianum* comes from the legend that the white veins running through the plant leaves were caused by a drop of the Virgin Mary's milk [3, 17].

Pharmacopeia name: Cardui mariae fructus [24]

## Taxonomy

| | |
|---|---|
| Kingdom | *Plantae* – Plants |
| Subkingdom | *Tracheobionta* – Vascular plants |
| Superdivision | *Spermatophyta* – Seed plants |
| Division | *Magnoliophyta* – Flowering plants |
| Class | *Magnoliopsida* – Dicotyledons |
| Subclass | *Asteridae* |
| Order | *Asterales* |
| Family | *Asteraceae* – Aster family |
| Genus | *Silybum* Adans. – Milk thistle |
| Species | *Silybum marianum* (L.) Gaertn. [6, 24] |

Milk thistle is one of the most important medicinal members of Asteracae family [3]. The genus contains two species: *S. marianum* (L.) Gaertn, with variegated leaves, and *S. eburneum* Coss. Et Durieux, with totally green leaves, but genetic investigations of these two species showed that they are only variants [7, 25]. A morphological description of the plant from different references is presented in Table 1 and Figure 1.

**Table 1- Morphological characteristics of milk thistle**

| Row | Morphological characteristics | Description, Color and Texture | Dimensions |
|---|---|---|---|
| 1 | Plant habit | High, erect [32, 33] | - |
| 2 | Stem | Stout, rigid, glabrous or slightly downy and not spiny, branched or unbranched [29, 32, 36] | 3 m [34], 40 – 200 cm [28, 32], 200 – 250 cm [35] |
| 3 | Leaf | Alternate, glossy, dark green with milk-white veins running throughout [2, 3]<br>Basal leaves: alternate, large, deeply lobed [2] and glabrous with spiny margins [28]<br>Stem leaves: alternate and smaller, clasp the stem [32], not quite as lobed [2] | Length: 75cm<br>Width: Up to 30 cm [6] |
| 4 | Spines | Woody [35] | Spines of leaves: 3 - 4.5 cm, Spines of bracts: 1.9 - 5 cm [3] |
| 5 | Root | One long taproot [3] | – |
| 6 | Receptacles | Including rows of broad, leathery bracts that are tipped with very stiff spines (1.9 - 5 cm) long and fringed with smaller spines [2] | 1.5 - 1.9 cm |

**Table 1- Continued**

| Row | Morphological characteristics | Description, Color and Texture | Dimensions |
|---|---|---|---|
| 7 | Inflorescence | Large and round capitula, solitary at the apex of the stem or its branches, surrounded by thorny bracts [2, 36] | Diameter of flower head: about 5 cm |
| 8 | Florets | Tubular, hermaphrodite [37] | 13 - 25 mm [4] |
| 9 | Number of achenes | - | 150 per capitulum, 6000 per plant [3] |
| 10 | Seed | Heavy, flat, smooth, and shiny, achene, with a white, silky pappus and color ranging from black to brown [33], glossy brown to black, with a cocoalike odor and oily taste [3] | Broad: 3 mm and thickness: 1.5 mm, length: 6 – 8 mm [26], pappus scales 15 –20 mm [4] |

**Figure 1- Milk thistle plant [30]**

In general, two types of *S. marianum* occur in some area of Asia including purple flowers and white flowers [26]. A single capitulum can produce up to 200 florets with color ranging from magenta to purple [26]. In cut transversely, the fruit shows a narrow, brown outer area and two large, dense, white oily cotyledons [27]. Also the fruits are an elaiosome, fleshy structure on fruit that is rich in lipid and is attractive to ants and thus aids seeds dispersal [28]. A significant dependence between the shapeliness of the fruits and the mass of 1000 fruits was indicated that biggest fruits had the highest mass and best vigour [29]. Seeds in the secondary flower heads had





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a conspicuously lower weight, when compared to the primary ones [28].

The plant size at the first bloom was reduced by postponing the sowing period from October to February. The same decreasing trend was observed in the number of flower heads and in the number of days required for the first bloom [28].

## Origin

Milk thistle is indigenous to the Mediterranean region and is widespread in Central Europe, Central and Western Asia, North Africa, North and South America and Southern Australia [2, 27]. The plant was carried to North America by European colonists during the $19^{th}$ century and is now naturalized in the United States and South America, Australia, China and Central Europe [7].

## Milk thistle in Iran

Milk thistle is commonly found in the provinces of Mazandaran, Gilan, West and East Azarbaijan, Kermanshah, Khuzestan, Fars and Bushehr [21]. In one of the experiments, Shokrpour et al. [31] compared milk thistle accessions coming from some provinces of Iran for quantitative and qualitative features (Table 2). These results showed considerable variation among the studied genotypes for the measured attributes.

## Ecology

Milk thistle adapts with different conditions climates. It can be cultivated in northern climates such as Canada as well as in southern and arid conditions [11], (Table 3) because it is hardy and adaptable [6]. Morazzoni and Bombardelli (1995), claimed that the highest content of silybin, the main component of silymarin, is found in plants from subtropical climates and not from moderate ones, because higher temperatures seem to enhance the accumulation of that compound [37, 38]. Milk thistle grows well and has good yield on different soil types [37, 38, 39]. Milk thistle is normally considered to be a weed that grows along roadsides and on wastelands [32] and reported as being a noxious weed in several countries because it competes with crops both for water and for nutrients [3]. Milk thistle proliferates best in nitrogen-rich media such as dairy yards, chicken coop waste, garbage dumps and abandoned agricultural fields [38].

The silymarin content in fruits depends on the milk thistle variety and geographic and climatic conditions in which they grow. However, the highest content of silybinin as the main component of silymarin, is found in subtropical climates rather than from temperate climates [21, 38].

**Table 2- Some characters of Iranian milk thistle accessions [31]**

| Characters | Lowest - Highest | Unit |
|---|---|---|
| Capitulum per plant | 11.85 (Dezfoul) - 26.9 (Ramhormoz) | Number |
| 1000 seed weight | 15.131 (Gharaghieh) - 22.73 (Dezfoul) | g |
| Stem height | 131.8 (Hamidieh) - 166.475 (Gharaghieh) | cm |
| Capitulum diameter | 3.775 (Andimeshk) - 4.48 (Jolgeh khalaj) | cm |
| Seed yield | 961.9 (Hamidieh) - 2239.7 (Parsabad) | kg $ha^{-1}$ |
| Seed weight per capitulum | 0.970 (Hamidieh) - 1.89 (Dezfoul) | g |
| Seed per capitulum | 51.64 (Hamidieh) - 95.89 (Naharkhoran) | Number |

**Table 3 - Some ecological factors of milk thistle growth**

| Factor | Descriptions and reports |
|---|---|
| Climate | - Adapts perfectly to different conditions of moderate subtropical climates<br>- Cool wetter conditions probably prolong the vegetative phase, resulting in fewer flowers in the seed dehiscing development stage at harvest [41] |
| Altitude | - Hilly environments produced a higher number of secondary flower heads compared with the plane site [28]<br>- 700-1100 m [38]<br>- In India in 1800 - 2400 m [6]<br>- 250-2400 m [36]<br>- In Iran, 0-420 m [40] |
| Soil | - Grows well and has good yield on different soil types [39, 41, 42]<br>- Deeper clay soil and very good supply of nutrients [43, 44]<br>- Sandy soils to much heavier clay soil [33]<br>- Growing well in soils with a pH of 5.5 – 7.6 [33] |

Milk thistle is a nitrate accumulator and can be lethal when livestock ingest the plant, particularly in the early wilting stage [40].

## Growing period

Milk thistle grows as a winter annual or biennial herb, depending on climate. Germination occurs in autumn and spring [7]. Studies have shown that milk thistle seed germination is affected by light and temperature conditions [32]. Fresh milk thistle seeds seem to need an after-ripening period and germinate better at low temperatures compare to high temperatures. The seeds remain viable for 9 years or more. Young (1978) expressed that the incubated seeds in higher temperatures need for the longer after-ripening period [45]. Mel'nikova (1983) reported that the minimum and maximum constant germination temperatures for *S. marianum* are 10 and 35°C, and optimum germination occurs at 20 – 25°C [45]. Ghavami and Ramin (2007) reported that the percentage of germination at 15°C was higher than in 25 and 35°C [46].

After seedling establishment, milk thistle overwinters as a rosette and in the meanwhile basal leaf number were increasing. In late winter and early spring, milk thistle enters into the flowering stage when it receives a stimulus from low temperatures. Flowers anthesis occure from April - May. The achenes (fruits) are ripe in July. The whole growth period of milk thistle was 125 - 140 day, which could be divided into seedling stage (15 – 20 day), vegetative stage including two stages: rosette stage and stem elongation (45 - 60 day), flowering stage, fruit bearing stages and withering stages [7].

Within a capitulum, anthesis usually lasted five days. Ripe fruits were released about 17 days later. Individual plants had the potential to produce an average of 55 capitulum [47]. A single seed head can produce around 100 - 190 seeds [39]. Flavonolignan accumulation in seeds depends on the stage of flower development and is maximum at the late flowering time [39].





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## Cultivation practices

Cultivation practices such as sowing date, fertilization and irrigation are important management factors in the production of all medicinal plants. In milk thistle, increased yield of the fruits along high silymarin content is an important aim for its cultivation. Omer and Ibrahim (1995) reported the nitrogen and especially potassium fertilization and plant spacing affected fruit yield and content of flavonolignans of milk thistle [49]. Andrzejewska and Sadowska (2007), showed that soil fertilization positively affected milk thistle fruit yield, silymarin content and proportion of unsaturated fatty acids [49]. However, soil rich in chemical fertilizers (nitrogen in particular) may have an adverse effect on the plant [41, 50]. Omidbaige (1991), showed that nitrogen fertilization had a significant effect on growth parameters of milk thistle. Nitrogen fertilization stimulates the growth of this plant but had significant negative impact on the silymarin and silybin content of the fruits [35]. In areas with high rainfall, nitrogen fertilizer can be applied regularly throughout the life cycle of the crop because it leaches from the root zone [33]. Milk thistle responds highly to moisture conditions. Both water excess and deficit inhibit silymarin accumulation. The highest silymarin level was recorded in plants grown at 60% field capacity [51]. Hassan et al. (1999) stated that irrigation and nitrogen fertilization (360 kg $ha^{-1}$) produced the most vegetation and the greatest number of flower heads per plant, but the maximum yield of fruits occurred when the plants had a moderate level of irrigation (60% of field capacity) combined with a suitable level of nitrogen fertilization [48].

The number of lateral branches produced on milk thistle plant depends on the density of plants and climate conditions. Milk thistle planted at the low density of 10 plants per square meter, formed 10 – 16 lateral branches. Also, silymarin content was affected by row spacing. Narrow row spacing of 25 cm increased the friut yield, but reduced oil and silymarin content compared to plants grown in rows 50 cm apart. Delayed sowing date causes the plant to reach the reproductive phase quickly at higher temperatures, which decreases the fruit yield but content of silymarin increases [52, 53, 54, 55, 56]. In summary, agronomic practices of milk thistle and relevant references for additional information reported in Table 4.

## Biotechnology

*Silybum marianum* (L.) Gaertn. is a diploid species with 2*n* = 34 chromosomes. Five of these chromosomes are of types “metacentric”, “sub-metacentric” and “acrocentric” [57, 58, 59]. Genetic improvements in milk thistle can only be achieved through a clear understanding of the plant’s behavior and the amount of variability presented in wild populations (ecotypes). [28, 33]. Silymarin samples from native ecotypes had lower quantities of silybinin as compared to that of silymarin from cultivated ones, but they had higher amounts of other compounds such as silychristin, silydianin and isosilybinin [60, 61].

The breeding studies for this plant are very low due to strong thorny stem, spiked leaves, flowers tipped with stiff spines [62]. In some countries such as Germany, a few varieties of milk thistle have been bred. Cultivar Silyb, was bred in the early 80’s [41]. In the 1990s,

**Table 4 - Some of milk thistle cultivation practices**

| Practice | Descriptions and reports |
|---|---|
| Soil preparation | The soil usually plows to 25 – 30 cm depth [36]. Before the sowing, rotary hoe cultivation is used to prepare a good seed-bed [33] |
| Sowing depth | 1 – 1.5 cm [33], 3 cm [36]. Plant emergence was strongly reduced from a depth of more than 3 cm [32] |
| Methods of sowing | Directly seeded in soils [33] |
| Spacing of sowing | Row spacing is usually 40 – 75 cm, with 20 – 30 cm between plants in the row [33, 37]<br>Rows 60 cm [36]<br>In Egypt 50 cm between hills [49]<br>In Spain, 40 – 50 plants per square meter [37]<br>In Germany, 20 – 30 plants per square meter [55] |
| Plant density | In warmer climates it is usually recommended that plants be planted at a much lower density than in moderate climates [49]<br>Row spacing is usually 40 – 75 cm, with 20 – 30 cm between plants in the row [49] |
| Seed rate | In Germany at 20 – 30 plants per square meter [38]<br>In Poland, 15 – 20 kg $ha^{-1}$ of seed [36]<br>Increasing the sowing rate of seed from 12 to 24 kg $ha^{-1}$ resulted significant increase in achene yield [36] |
| Seed yield | Seed yield of plants cultivated in clay soil was superior to that of plants on sandy soil in both seasons [56]<br>In Poland, especially on good soils the average yields are 1000 – 1700 kg $ha^{-1}$ [49] |
| Time of Sowing | In autumn and spring [29]<br>In Italy sown in late autumn [41]<br>In Iran, September [34]<br>In New Zealand, in late summer [25] |
| Irrigation | Drought resistant and normal rainfall will often suffice [36]<br>In a Mediterranean environment, under severe drought conditions, the crops should be irrigated during seed growth and filling [33] |

**Table 4 - Continued**

| Practice | Descriptions and reports |
|---|---|
| Fertilizer | Low to moderate [33]<br>Potassium and phosphorus are generally applied pre-sowing<br>In Poland: 50 kg $ha^{-1}$ N, 30.5 kg $ha^{-1}$ P and 58 kg $ha^{-1}$ K before sowing [36]<br>In Bulgaria, 49.5 kg $ha^{-1}$ N, 138 kg $ha^{-1}$ $P_2O_5$ and 150 kg $ha^{-1}$ $K_2O$ to the soil before sowing [43]<br>In Czech Republic: 45 - 60 kg $ha^{-1}$ N, 17.5 kg ha-1 P and 33.2 kg $ha^{-1}$ K<br>In Egypt: 120 - 240 kg $ha^{-1}$ N, and 62 kg $ha^{-1}$ P [50] |
| Growth regulating | Treatment of milk thistle with plant-growth regulators in combination with soil or foliar mineral fertilizers increased the total amount of silymarin by increasing seed yield per hectare [43] |
| Weed control | Pendimethalin and metribuzin herbicides are safe for weed control, both alone and in combination [33] |
| Rotation | The milk thistle is recommended for incorporation into arable crop rotation as forecrop of maize [50]<br>The rotation could be planned preferring spring-summer crop. During these seasons, milk thistle is smaller and therefore less competitive [36]<br>Yields of milk thistle grown in an monoculture were about 40% lower than the yields obtained in crop rotation that the yield decrease was mainly due to root damage caused by larvae insect (*Cleonus* piger) [52] |
| Harvesting | Harvest with the use of combined harvester, when 40-50% of inflorescences have pappus [51]<br>In July – August after blooming [43] |

the Silma cultivar was bred and registered in Poland [37]. Ram et al. (2005) analyzed the genetic variability of 15 accessions of milk thistle based on morphological characteristics and silymarin content and reported considerable variation in silymarin concentration [43]. Hetz (1995) reported that silybum is predominantly a self-pollinator, since the cross-pollination rate on average is only about 2% [25].

In vitro cultures have been used as an alternative source of biologically active compounds [60, 61]. Studies on culture of milk thistle in vitro began in the late 1970s [7]. Tissue culture protocol have been established for milk thistle from cotyledons and sterile plantlets to induce callus on Murashige and Skoog medium (MS) supplemented with different hormones. Optimum results obtained with the use of naphthalenee acetic acid and





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kinetin [62, 63]. Liu and Cai referred to the isolation and culture of protoplasts [64]. Cotyledon cultures have employed to produce organogenesis and somatic embryogenesis in milk thistle [65]. Production of flavonolignans from transformed (hairy) and untransformed root cultures of *Silybum marianum* also was reported [66]. Elicitors have been widely employed to increase the formation of secondary metabolites in plant cell cultures and this strategy has also been effective in stimulating the production of silymarin in cell cultures derived from milk thistle [67]. Production of silymarin and the effect of the elicitor, methyl jasmonate (MeJA), were studied in cell cultures of *Silybum marianum* [68].

Treatment of *S. marianum* suspensions with a crude extract of yeast elicitor (YE) improved the production of silymarin and caused the release of silymarin into the culture medium to a level about threefold higher than that of the control. The yeast extract and methyl jasmonate (jasmonic acid derivatives), strongly promoted the accumulation of silymarin [67, 68]. Hansaloo et al. (2006), reported the effects of jasmonic acid on silymarin production in milk thistle cultures [69]. Yeast extracts stimulated flavonolignan production in hairy root cultures two fold higher than the control cultures. Moreover, it was reported that the yeast extract treatment induced the activity of lipoxygenase for production of the jasmonate. It was concluded that jasmonate signaling is an integral part of the yeast extract signal transduction for the production of flavonolignans [70]. Besides improving production, elicitation allows the study of signal transduction pathways which regulate the expression of biosynthetic genes involved in plant secondary metabolism [7, 70]. Rahimi et al. (2011) studied the effect of different concentrations of L-phenylalanine (0, 1, 10 and 100 μM) as the precursor, on thephenylalanine ammonia-lyase activity, naringenin content, root biomass and silymarin production in *Silybum marianum* hairy roots. All concentrations of added phenylalanine stimulated phenylalanine ammonia-lyase activity [71]. In a study the effect of abiotic elicitors, two newly synthesized substituted amides of pyrazine-2-carboxylic acids on the flavonolignan accumulation in callus and suspension culture of *Silybum marianum* (L.) Gaertn. was investigated. The compounds markedly influenced the production of flavonolignans in an in vitro culture [72].

## Pharmacological applications

The pharmacological active ingredients present in milk thistle fruits collectively are known as silymarin. Silymarin contains structural flavonolignan isomers: silybin (silibinin) (50 - 60%), isosilibinin (5%), silicristin (20%), silidianin (10%) and other components such as taxifolin (5%) (Figure 2) [60]. Other constituents include apigenin, silybonol, dehydrosilybin, deoxysilycistin, deoxysilydianin, silandrin, silybinome, silyhermin, and neosilyhermin [2, 3, 73]; It has been reported that milk thistle fruits have a relatively high amount of oil (20–31%) [74, 75, 76] that contains fatty acids such as linoleic acid, oleic acid, linolenic acid, palmitic acid, stearic acid. Silybin is the major biologically active constituent of milk thistle and responsible for its pharmacological activity. It has been used for centuries to self-treat liver disorders [3, 74].

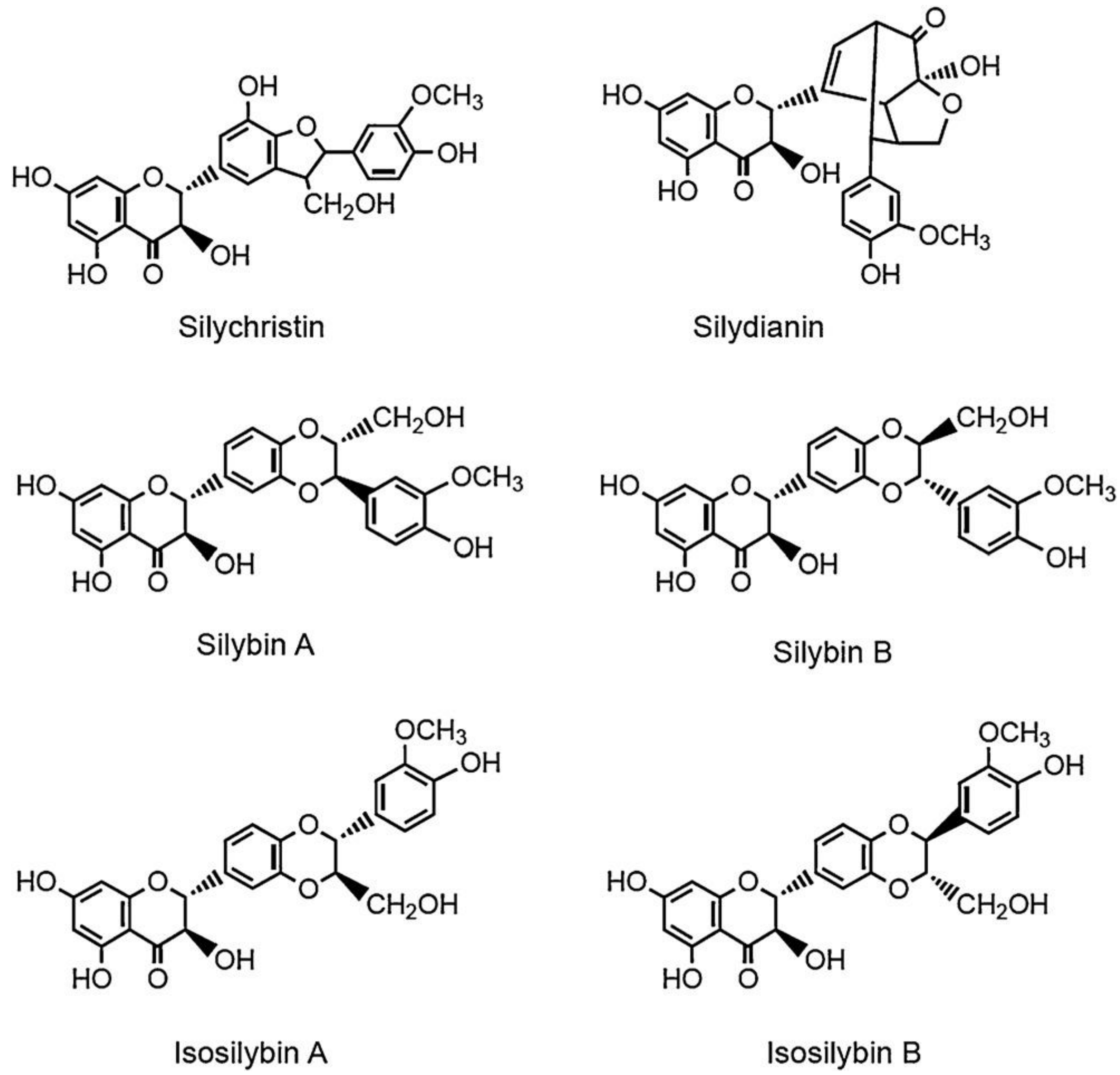


**Figure 2- Chemical compositions of milk thistle [7]**

Milk thistle is used for multiple medicinal purposes, due to its various physiological characteristics. Research has confirmed that silymarin extracted from milk thistle fruits can protect healthy liver cells from deterioration, helping cleanse and detoxification, as well as contributing to regeneration of damaged cells [3, 77].

Various components of milk thistle (silymarin, silybin, etc.) have multiple mechanisms of action that may be hepato-protective, including anti-inflammatory activity, antioxidant activity, toxin blockade, enhanced protein synthesis and anti-fibrotic activity [77, 78]. As mentioned, the main action of the active principles of *S. marianum* is hepatoprotective. A summary of the effective pharmacological applications milk thistle included hepatoprotective action, alcoholic liver diseases, viral hepatitis, liver cirrhosis [79, 80], toxic and drug diseases of the liver, mushroom poisoning, diabetes patients with chronic liver disease and hypocholesterolemic action [3, 79].

**Antioxidant properties**

The antioxidant properties of milk thistle were evaluated by studing the ability to react with relevant biological ROS or oxidants such as superoxide anion radical ($O_2$), hydrogen peroxide ($H_2O_2$), hydroxyl radical ($OH^-$) and hypochlorous acid (HOCL). Kiruthiga et al [81] have shown that administration of silymarin increases the activities of antioxidant enzymes like superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione-s-transferase (GST) together with a decrease in the levels of malondialdehyde (MDA), a marker for lipid peroxidation, in erythrocytes exposed to $H_2O_2$ [82].

**Anti-inflammatory Activity**

Anti-inflammatory effects of silymarin are related to inhibition of the transcription factor nuclear factor-κB (NF-κB), which regulates and coordinates the expression of various genes involved in inflammation, cell survival, differentiation and growth [82].

**Mushroom Poisoning**

The most remarkable use of silymarin is in the treatment of Amanita mushroom poisoning. Amanita mushrooms possess two extremely powerful hepatotoxins, amanitin and phalloidin. Severe liver damage (and death) was avoided if silymarin was administered within 24 hours [83].

**Alcoholic liver diseases**

Research on *In Vitro* and *In Vivo* animal models suggested that silymarin has ability to protect liver cells from toxins. In alcoholic liver diseases (ALD), silymarin was found to exert hepatoprotective effects by attenuating the tumor necrosis factor (TNF) production along with decreasing the serum alanine aminotransferase (ALT) activity, inhibiting lipid peroxidation, and increasing the intracellular reduced glutathione content in mouse model of ALD [84]. A double-blind study achieved on patients suffered from chronic alcoholic liver disease. The result demonstrated that serum bilirubin, aminotransferase values and gamma glutamil transferase (GGT) activity were normalized in the silymarin group [85].

**Anti-cancer Activity**

Carcinogenesis is a multistep process that is activated by altered expression of transcriptional factors and proteins involved in proliferation, cell cycle regulation, differentiation, apoptosis, angiogenesis, invasion and metastasis. Silymarin and silybin modulate imbalance between cell survival and apoptosis through interference with the expressions of cell cycle regulators and proteins involved in apoptosis [82].

Anti-cancer activity of silymarin has been demonstrated in human breast cancer, skin cancer, androgen-dependent and -independent prostate cancer, cervical cancer, colon cancer, ovarian cancer, hepatocellular carcinoma, bladder cancer, and lung cancer cells [82, 86, 87, 88].

**Anti-diabetic Activity**

The property of silymarin in reducing fasting glycaemia and insulin level have supported its use as an antihyperglycaemic compound. The potent hypoglycaemic and antihyperglycaemic activities of an aqueous extract of milk thistle have also been demonstrated in experimental animal models of diabetes [89, 90].





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### Hepatoprotective Activity

Silymarin has been used for centuries as a hepatoprotectant [91]. This effects have been attributed to direct and/or indirect anti-oxidant capacity of silymarin, such as being scavenger of reactive oxygen species, scavenger of phenylglyoxylic ketyl radicals, chain breaking antioxidant [83].

### Hypocholesterolaemic Activity

Survey the influence of silymarin and its polyphenolic fraction on rats fed with a high-cholesterol diet showed that silymarin reduced cholesterol levels in the liver and plasma of rats [92].

The hypocholesterolaemic activity of silymarin on the basis of experimental evidence showing that silybin inhibits HMG-CoA reductase activity in vitro; and silymarin improved the binding of low density lipoproteins (LDL) to rat hepatyocytes, decreased the liver cholesterol content in rabbits fed with a high-cholesterol diet, decreased the plasma-cholesterol and LDL-cholesterol levels in hyperlipaemic rats. The influence of silymarin and polyphenolic fraction (PF) of silymarin on cholesterol absorption in rats fed on high cholesterol diet (HCD) was studied. Silymarin and PF significantly reduced cholesterol absorption in rats fed on HCD and caused significant decreases in content of cholesterol and triacylglycerol (TAG) in the liver. These results suggest that the inhibition of cholesterol absorption caused by silymarin and its polyphenolic fraction could be a mechanism contributing to the positive changes in plasma cholesterol lipoprotein profile and in lipid content in liver [93].

## Conclusion

Milk thistle is one of the most important medicinal plants grown in the world. Silymarin is the pharmacological active principle of the fruit of this plant. The seeds contain the highest amount of silymarin, but the whole plant is used medicinally. Despite the world demand of silymarin, there is a lack of research efforts on the domestication and improvement of this plant especially in Iran. A few varieties of milk thistle have been developed. Our knowledge of agronomic practices and genotype-environment interactions which could promote high quality and quantity of milk thistle production under Iranian growth conditions is very limited. It is essential to define to what extent agrotechnical practices can affect the quality and quantity of silymarin.

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