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An insight into medicinal and therapeutic potential of *Silybum marianum* (L.) Gaertn

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Abstract

Silybum marianum (L.) Gaertn. member of family Asteraceae is considered as an important medicinal plant throughout the world. It is indigenous to Asia and North Africa. *Silybum marianum* is well known for its hepatoprotective, antidiabetic, anticancerous, antilipemic and antidote activities. In allopathic and herbal system of medicine it is useful for curing many ailments such as liver disorders, diabetes, hemorrhoids, psoriasis, cancer and female problems. All medicinal applications of Milk thistle are due to active constituent silymarin which is present in higher concentration in seeds as compared to other plant parts. Apart from curing human diseases this plant play an important role as veterinary medicine and also used in several cosmetic formulations such as body creams and lotions. Ethnobotanically the entire plant is used as vegetable due to its nutritional value. This paper gives an overview of scientific literature available on plant *Silybum marianum* (L.) Gaertn.

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Introduction

Geographical distribution

Silybum marianum is an important plant native to southern Europe, mainly to the Mediterranean regions, also indigenous to Asia, North Africa and Southern Russian Federations. It is now naturalized throughout Europe and North and South America, Australia. In subcontinent, it is found in Jammu and Kashmir and in Pakistan *S. marianum* is abundant in Khyber PukhtoonKhwa and Punjab (Bisset, 1994). Mostly it grows as weed on unutilized lands especially along road sides (Ngoddy and Ihekoronye, 1967).

Taxonomic position and morphology of plant

Species	<i>Silybum marianum</i> (L.) Gaertn.
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Taxonomic and Phenological Description

This plant has many common names such as Holy thistle, Marian thistle, Mary thistle, milk thistle, Our Lady's thistle, St. Mary thistle, wild artichoke, Marien distel, Chardon-Marie (Peirce 1999 ; Brinker 1997).

Silybum marianum (L.) Gaertn is a herbaceous plant belonging to the carduae tribe of the Asteraceae (daisy) family. Its synonym is *Cardus marianus* L. The common name, milk thistle, is derived because of the white markings (variegation) on the leaves which, when breaks open, yield a milky sap. The plant has erect, ridged and branched stem normally 20 to 150 cm in height, reaching to the height of 10 feet bearing large, alternating, prickly-edged, hard green, shiny leaves (Figure 1). Each stem ends with solitary composite flower heads, about 2 inches in diameter, consisting of purple disc florets due to presence of leathery bracts that are tipped with stiff spines. Flower head of *Silybum marianum* differ from other thistles (Figure 2). The fruits of milk thistle are smooth, shiny dark brown in color and hard skimmed achenes, 6 to 8 mm long flat. Seeds bear white silky pappus and are black to dark brown in color (Sidhu and Saini, 2012) (Figure 3). Flowering season is from June to August, and each stem bears a single, large, purple flower ending in sharp spines. The fruit portion of the plant is glossybrown or grey with spots (Bisset, 1994; Luper, 1998).

Chemical constituents

Fruits of *Silybum marianum*(L.) Gaertn. contain silymarin which is an isomeric mixture of flavonolignans (Morazzoni and Bombardelli, 1995). About 65 – 80% silymarin is present in its crude extract of dried seeds. Silymarin is a complex of about seven flavonolignans such as silybin A and B, isosilybin A and B, isosilychristin, silydianin and silychristin and the flavonoid taxifolin. Among these Silybin, isosilybin, silychristin and silydianin are principle components of silymarin (Figure 4). The isosilybins and, Silybins are isomers. Silybin is also known as silibin. It is regarded as the main active ingredient of the milk thistle. Other flavonolignans identified in milk thistle include dehydrosilybin, deoxysilydianin, deoxysilycistin, silybinome, silandrin, neosilyhermin and silyhermin. Beside these apigenin; silybonol; myristic, olie, palmitic and stearic acids; and betaine hydrochloride (which may have a hepatoprotective effect) are also identified in milk thistle (Varma *et al.*, 1980). All the properties of milk thistle are due to these flavonolignans combined with other ingredients (Cheung *et al.*, 2010).

Biological activities

Silybum marianum (L.) Gaertn. contains various phytochemicals. Almost all parts of milk thistle such as leaves, fruits and seeds contain silymarin in which silybin is the most biologically active constituent. Its fruits are rich in Silymarin (flavanolignans silybin, silydianin, and silychristine) where as seeds contain betaine, trimethylglycine and essential fatty acids. All the biological activities of milk thistle are due to the presence of these phytochemicals.

Hepatoprotective activity

Silymarin extracted from the *Silybum marianum* is mostly utilized by patients suffering from liver diseases. It was also proved to be highly effective for the patients of liver cirrhosis that resulted from the excessive use of alcohol. However the mechanism of its action is not fully known. It competes with toxins for hepatocyte binding and penetration. Basic clinical trials showed that milk thistle is beneficial for patients suffering from alcoholic cirrhosis but more

research and detailed experimental studies are required to draw any conclusion about its action (Boerth and Strong 2002). Different formulations of Silymarin are prepared by encapsulating them in lipid microspheres. The potential of Silymarin is found to be increase in lipid microspheres that's why capsules of Silymarin are prepared in lipid microspheres. The administration of Silymarin by this method further enhances the hepatoprotective effect of drug molecules (Abrol *et al.*, 2005). Its effect was tested on hepatotoxicity induced rats and their finding proves the hepatoprotectivity of these extracts against hepatic cell injury induced by Thioacetamide (Madani *et al.*, 2008).

Anti-hepatotoxic

Consumption of alcohol is becoming a societal problem now days, its excessive intake may cause health related problems in human being. Certain studies on rats have shown that the introduction of milk thistle protect the rats fetus from the damaging effects of ethanol being given to them (Busby *et al.*, 2002).

Silymarin and its flavonolignans present in *Silybum marianum* show cytoprotective activity. Investigations revealed that the different concentration of protective agents has different effect on toxic stimuli. Silymarin had cytoprotective effects on mouse liver cells, rat tracheal tissues and human testicular cancer cell lines exposed to carcinogens. It has ability to quench free radicals that are produced during infections and are harmful to the hepatocytes (Dvorak *et al.*, 2003).

Silymarin is quite useful to protect their unborn foetus from side effects of alcohol if pregnant patients are unable to avoid alcohol. Silymarin only mitigates some of the damages caused by the alcohol. The combined administration of Silymarin and garlic extracts has been proved to be more beneficial than individual extract administration in NDEA-induced hepatotoxic rats. These studies show that these plant extracts can be used successfully as hepatoprotective agents (Shaarawy *et al.*, 2009).

Anti-cancer activity

In the developing world the rate of cancer survival is poorer, may be limited assess of proper treatment or due to late diagnose. However, the risk of cancer can b reduced by making the people aware about cancer causing agents, and its proper treatment, by promoting physical activities and taking balanced and high nutritional value diet (Jemal and Bray, 2011).

Earlier *S. marianum* was used for detoxification and cleansing of body. In present days it used in cancer research. It is also used, during and after chemotherapy, to reduce risk of hepatotoxicity.

Silybum marianum extract reduce the side effects of radiodermatitis to a great extent. Naturally occurring polyphenolic antioxidants obtain from *Silybum marianum* are recognized as one of the most effective classes of cancer preventive agents (Agarwal, 2000; Marchand, 2002). The anticancer activity of Silymarin is mainly due to its chief constituent-silibinin (Bhatia *et al.*, 1999). It decreases the activity of tumor promoters, protects the genome and stabilizes most cells (Flora *et al.*, 1998).

Silymarin isolated from *Silybum marianum* lowered the harmful effects of chemotherapy. The researchers may develop mechanisms to treat cancer directly from *Silybum marianum* as Silymarin is known to be an anti-metastatic (Ramasamy and Agarwal, 2008).

Silybum marianum could be an ideal cancer preventive agent as it has high efficacy, no toxic effects, low cost, known mode of action and above all the human acceptability. Doses of *Silybum* are available in the market in certain developed countries. In developing countries like India, research is going on for its pharmaceutical utilization and commercial.

Anti-diabetic activity

The aqueous extracts of *Silybum marianum* aerial parts found to be the powerful hypoglycemic agents in diabetic as well as normal rats without altering the secretion of insulin. However, exact mechanism of action along with toxicological effects, is still wanted (Maghrani *et al.*, 2004). The patients treated with

Silymarin showed improved glycemic profile. Further detailed investigations are needed for this complementary therapy. (Huseini *et al.*, 2011).

Another study revealed the antiapoptotic and anti-inflammatory properties of *Silybum marianum* treatment of steatohepatitis (fatty liver) in rats. Histopathological examinations show that the crude extract of *Silybum marianum* subside the severity of non-alcoholic steatohepatitis (NASH) (Aghazadeh, 2011).

Wounds of diabetic induced rats treated with Silymarin ointment had shown reduced wound size as compared to the other group of rats. The ointment contains Silymarin which is effective in the treatment of diabetic rats. However, to investigate the actual active compound responsible for this action further detailed phytochemical analysis is required (Aliabadi *et al.*, 2011).

The effect of silymarin studied on the glycemic control of diabetic patients and after clinical studies it is reported that the average fasting blood glucose level in the silymarin group at the beginning of the study was reported as 156} 46 mg/dL, which decreased significantly ($p < 0.001$) to 133}39 mg/dL after 4 months of silymarin treatment (Huseini *et al.*, 2006).

Antidote activity

Silymarin has strong antidote activity against mushroom poisoning. Silymarin in combination with benzyl penicillin is quite effective against mushroom poisoning (Pradhan and Girish, 2006). Silymarin blocks the entry of amatoxin into the hepatocytes (Faulstich *et al.*, 1980). It also inhibits the entry of α -amanitin which is the most toxic form of amatoxin present in *Amanita phalloides* into the blood by combating its transport system (Faulstich *et al.*, 1980).

Antilipemic Activity

In vitro data suggested that silybin decreased cholesterol synthesis in rat liver homogenates (Schriewer and Rauen, 1977). Perfused livers taken

from rats and fed with a high cholesterol diet, silymarin normalized the cholesterol level by clearance of low density lipoproteins. Rats fed with high cholesterol diet when given with silymarin show improved hepatic LDL clearance. (Skottova and Krecman 1998). Similarly animal data suggested that silymarin provided significant protection against dietary-induced hypercholesterolemia in rats (Krecman *et al.*, 1998). In rats, biliary excretion of cholesterol salts 60-70% reduced by silybin but biliary flow rates remained unchanged (Nassuato *et al.*, 1983). Silymarin also exerted anti-atherosclerotic effects in rabbits that were fed with high cholesterol diets (Bialecka, 1997).

Human data suggest that in patients suffering from hypercholesterolemia, silymarin inhibit hepatic synthesis of cholesterol. It is suggested that the products of milk thistle should be investigated as a treatment for patients with hypercholesterolemia (Skottova and Krecman, 1998).

Silymarin was also evaluated for its anti-inflammatory and antiarthritic activities against inflammation and arthritis in rats. It show significant anti-inflammatory and antiarthritic activities through the inhibition of 5-lipoxygenase (Gupta *et al.*, 2000). The oral administration of Silymarin can reduce the carrageenan-induced paw oedema in rats. It can also reduce inflammation of mouse ear (induced due to harmful toxins) therefore, *Silybum marianum* very much comparable to indomethacin (De LaPuerta *et al.*, 1996).

So after all that laboratory experimentation, it was concluded, Milk thistle can be used as an alternative medicine for hepatic inflammation but cannot be recommended as a general anti-inflammatory agent. There are some practitioners who prefer to use *Silybum marianum* to cure the inflammation of the joints, particularly in the case of wrists (Mitchell, 2003).

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Medicinal uses

In Europe since 1st century *Silybum marianum*(L.) Gaertn has been used for medicinal purposes. It was

first reported by Theophrastus (Schuppan *et al.*, 1999). Pliny claimed that it is helpful in improving bile flow. This plant was also mentioned in the writings of Culpepper, Jacobus Dioscorides and Theodorus (Luper, 1998).

In Traditional Chinese Medicine the seeds of milk thistle are known as *Shu iFei Ji*. It helps to increase bile secretion also used for treatment of liver problems in china. Ripened seeds are used to treat many hepatobiliary ailments, such as jaundice, hepatitis, gallstones, cirrhosis as well as for curing kidney problems (Fintelmann, 1991).

For 2000 years the mature untreated seeds of milk thistle have been used in traditional medicine to treat headache, melancholy, detoxification, digestive and liver complaints. It is also recommended by some herbalists to treat insufficient lactation. (Wichtl, 2004; Braun and Cohen 2010). This plant is also recommended by German Commission E for the treatment of dyspeptic complaints, toxin-induced liver damage, and hepatic cirrhosis and for therapy in chronic inflammatory liver conditions. (Blumenthal 1998).

The medicinal properties of *Silybum marianum* (L.) Gaertn were highlighted in several historical evidences. It acts as treatment for Alzheimer's disease, also possessing anticarcinogenic, anticirrhotic and antidepressant properties. It is also used as antidote to mushroom poisoning, as a galactagogue, as an emetic and for control of food and seasonal allergies. In traditional systems of medicine it is used to treat cough, dyspepsia, eczema, elimination of abscesses, gallbladder disorder, gastrointestinal problems, hypocholesterolaemic, immunity enhancement, kidney disorders, liver disorders, lung ailments, migraine, motion sickness, psoriasis, skin and spleen disorders, skin cancer, sweat inducing, to cure constipation, to cure menstrual problems, tonic and diuretic and treating infections *etc.*(Corchete, 2008). Some of its key medicinal properties are highlighted below.

Mushroom Poisoning

Treatment of *Amanita phalloides* mushroom poisoning is the most impressive use of silymarin. The genus *Amanita* is widespread in North America and Europe mutually growing with numerous edible mushrooms. Many of the *Amanita* species are highly toxic. Unfortunately, in about 30 percent of cases, ingestion results in liver damage and death (Vogel *et al.*, 1984). In animal studies, silymarin completely counteracted the toxic effects when given within 10 minutes after *amanita* toxin ingestion, and if given within 24 hours of toxin ingestion silymarin prevented death (Desplaces, 1975).

Hepatitis

In the treatment of both acute and chronic hepatitis silymarin was found to be very much effective. Its administration have shortened treatment time and lowered serum bilirubin, AST, and ALT. In acute viral hepatitis, administration in 420 mg silymarin per day for six months also yielded improved serum liver enzymes in patients with chronic hepatitis (Magliulo *et al.*, 1978).

Hypercholesterolemia

An animal study found that silymarin is found to have an anticholesterolemic effect similar to probucol, with an increase in HDL cholesterol and a decrease in total and biliary cholesterol when given to rats with diet-induced hypercholesterolemia demonstrated (Krecman *et al.*, 1998).

Psoriasis

For the treatment of psoriasis, the value of silymarin is may be due to its ability to inhibit cAMP phosphodiesterase by improving endotoxin removal by the liver and inhibiting leukotriene synthesis. Abnormally in patients with psoriasis, high levels of cAMP and leukotrienes have been observed (Fiebrich and Koch 1979; Kock *et al.*, 1985).

Curing Female Problems

Silymarin is considered as wonder drug for women. The fruits of milk thistle have been used by the nursing mothers to increase the milk production. But

its mode of action is not clear. In this way, Silymarin can be considered a good candidate to overcome the lactation deficiency (Capasso *et al.*, 2009). It increased the level of prolactin in the serum, considerably after giving treatment for specific days. It is also used for the treatment of menstrual disorders and for relieving the pain of menstrual cycle. That's why; females prefer to consume it orally in the form of capsules (Kapoor *et al.*, 2009).

Pharmacokinetic properties

Silymarin is not water soluble that's why making tea preparations ineffective therefore it is usually administered orally in encapsulated form. It is best administered as a standardized extract of 70-80 percent silymarin because absorption of silymarin from the gastrointestinal tract is only moderate (23-47%). after an oral dose in both animals and humans, peak plasma levels are reached in four to six hours. Silymarin is excreted mainly through the bile but some clearance is also achieved by means of the kidneys. The clearance half-life of silymarin extract is six to eight hours (Vogel *et al.*, 1984).

Toxicity and some contraindications

Allergic reactions

Allergic reactions to milk thistle are reported. One case reports a British woman who in fact had a severe allergic reaction to a milk thistle capsule but it was unclear that whether the reaction was due to milk thistle or some other ingredient in the capsules. However, potentially toxic compound in milk thistle is not yet identified. There are some reports establishing that it causes gastrointestinal disturbances and skin allergies (Bean, 2002).

Acute toxicity

According to some herbalists, a mild laxative effect of milk thistle might be experienced if it is given orally. This effect is experienced due to its stimulating effect on the liver and gallbladder. However, in numerous randomized studies, side effects from milk thistle have not been any greater than with placebo. Silymarin has not had considerable adverse effects in animals even when given in very high dosages. In a

series of several thousand patients, the rate of side effects was very low and restricted primarily to mild gastrointestinal upset (Albrecht, 1992).

Long term use during pregnancy and childhood

During pregnancy, lactation and childhood The safety of long-term use of milk thistle has not been established, but based on its long historical use as a food it is assumed safe (Giannola *et al.*, 1985).

Veterinary medicines

Silybum drug is used for making animals fat and for increasing their body weight. Its seed cakes were added to the chick feed. Silymarin also increased the hatchability in chickens and turkeys. Silymarin increases the glycogen and reduces the lipid contents content thereby acting as hepatoprotective agent (Suchy *et al.*, 2008).

Silymarin can improve the meat quality. It enhanced muscles' resistance to oxidative stress but has not shown any hepatoprotective effect (Schiavone *et al.*, 2007). Silymarin was investigated for its hepatoprotective activity in white pigeons (*Columba livia*) challenged with B1 aflatoxin. It has not shown any hepatoprotective effects during Histopathology and hepatobiliaryscintigraphy studies. However, the intake of aflatoxin resulted in hepatic necrosis,

inflammation, lymphocyte infiltration and biliary-duct hyperplasia (Grizzle *et al.*, 2009).

While grazing in the fields the ruminants sometimes ingests the sawfly larvae (*Argepullata*) which cause hepatotoxicity compound isolated from *Silybum marianum* have been proved effective in the treatment of hepatotoxicosis caused by sawfly larvae in ruminants (Thamsborget *et al.*, 1996).

Silymarin is also usefull in the treatment of *Giardia* parasitosis in dogs where the use of antibiotic, metronidazol causes hepatic disorders. In a study it was observed that as compared with the positive control group in which these indicators has significantly increased which proved the importance of Silymarin in curing liver diseases the dogs treated with Silymarin had shown normal level of serum indicators of liver inflammation (Chon and Kim, 2005).

Ethnobotanical uses

The name pternix was given to milk thistle by Theophrastus in the 4th century B.C. Historically, whole plant was used as vegetable with no toxic side effects, roots was also eaten as nutritional supplement (Karkanis *et al.*, 2011). Its seeds were made into decoction to treat hemorrhoids while infusion of seeds act as diuretic (Pausalacqua *et al.*, 2007).

Table 1. Taxonomic Hierarchy of *Silybum marianum* (L.) Gaertn.

Kingdom	Plantae
Subkingdom	Viridiaeplantae
Infrakingdom	Streptophyta
Division	Tracheophyta
Subdivision	Spermatophytina
Infradivision	Angiospermae
Class	Magnoliopsida
Superorder	Asteranae
Order	Asterales
Family	Asteraceae
Genus	<i>Silybum</i>
Species	<i>Silybum marianum</i> (L.) Gaertn.

Other uses

Constituent of cosmetics

In cosmetics, it is used in different body creams and lotions to protect the body from various skin

infections. The Silymarin is used as an antioxidant. Besides its application in pharmaceutical, food industry and agricultural, it has been used in various cosmetic products (Malhotra and Singh, 2003).

Silymarin has been used as herbal constituents of photoprotective agents. Now days, Researchers are looking for new safe, alternative, economical and more effective herbal photoprotective cosmetic formulations (Chanchal and Swarnlata, 2009).



Fig. 1. Plant body.



Fig. 2. Floral part.

Tea Preparation and roasted seeds

Silymarin is poorly soluble in water, *Tea* is not the preferred route of administration since but if the seeds of milk thistle are roasted and broken open they can be used as tea. The usual dose is 12-15 grams of roasted, cracked seeds.



Fig. 3. Seeds.

Conclusion

Milk thistle is used for treatment of many ailments in allopathic and herbal system of medicine such as liver disorders, diabetes, hemorrhoids, psoriasis, cancer and female problems. Its medicinal properties are due to presence of an isomeric mixture of flavonolignans known as silymarin and it is considered as one of the favored drug in entire world. It has various biological activities such as hepatoprotective, anticancer, antidiabetic and antilipemic activities. It also acts as antidote for mushroom (*Amanita phalloides*) poisoning. It is considered as an important plant in terms of veterinary medicine. Silymarin has been used in various cosmetic products such as in different body creams and lotions and protect body from various skin infections. Its high dose causes the gastrointestinal troubles, allergic reactions. Its long term use is not recommended in pregnancy and childhood. Compound responsible for toxic activities of milk thistle havenot been identified yet, so there is need of further research to identify that specific compound. Traditionally entire plant has been used as vegetable and its root is considered as nutritional supplement. Since *Silybum marianum* has numerous historical and current medicinal applications, it should be tested further. More studies are required in future in order to reveal the new efficient treatments for health problems.

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