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Review Article

Silybum marianum (Milk Thistle): Review on Its chemistry, morphology, ethno medical uses, phytochemistry and pharmacological activities

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ABSTRACT

The oldest remedies identified to mankind are herbal medicines. India is recognized worldwide for its Ayurvedic treatment. India has rich history of using many plants for medicinal purposes. Remedial plants are cooperating extremely dynamic position in customary drugs for the action of a variety of illness. However a key obstacle, which has hindered the promotion in use of alternative medicines in the developed countries, is no evidence of documentation and absence of stringent quality control measures. There is a demand for the evidence of every investigate effort execute on conventional remedies in the appearance of certification. The purpose of current review is to make accessible up-to-date information on, botany, morphology, ecological biodiversity, therapeutic uses, phytochemistry and pharmacological activities on diverse parts of *Silybum marianum* (L.) Gaertn (*S. marianum*). This review was assembled using technical literature from electronic search engine such as Springer link, Bio Med Central, Pub Med, Scopus, Science Direct, Scielo, Medline and Science domain. Supplementary texts were obtained from books, book chapters, dissertations, websites and other scientific publications. *S. marianum* a member of the Asteraceae family, is a tall herb with large prickly white veined green leaves and a reddish-purple flower that ends in sharp spines. It is native of the Mediterranean region and which has also spread in East Asia, Europe, Australia and America. It is grown as a commercial crop in several countries, including Iran and Pakistan. Confident chemical constituents were exposed cognate as silybin A, silybin B, isosilybin A, isosilybin B, silychristin, silydianin, apigenin 7-O-β-(2"-O-α-rhamnosyl)galacturonide, kaempferol 3-O-α-rhamnoside-7-O-β-galacturonide, apigenin 7-O-β-glucuronide, apigenin 7-O-β-glucoside, apigenin 7-O-β-galactoside, kaempferol-3-O-α-rhamnoside, kaempferol, taxifolin and quercetin. The plant is exclusively used as anti-diabetic, hepatoprotective, hypocholesterolaemic, anti-hypertensive, anti-inflammatory, anti-cancer, and as an anti-oxidant. Seeds of the plant are also used as an anti-spasmodic, neuroprotective, anti-viral, immunomodulant, cardioprotective, demulcent and anti-haemorrhagic. The plant is also serves as a galactagogue, agent that induces milk secretion and used in the treatment of uterine disorders. The plant is employed in dissimilar conventional schemes of remedy in the cure of different illness. The present paper enumerates the Pharmacognostic, morphological and ethnobotanical, pharmacological importance of the *S. marianum*, which may help the researchers to set their minds for approaching the utility, efficacy and potency of the plant.

Keywords: Medicinal plants, *Silybum marianum*, Asteraceae, Phytochemistry, Pharmacological

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Introduction

Plants are used for a variety of purposes. The history of natural products is relatively old and dates back to the time when the early man became conscious of his environment. Cultured and civilized man is said to have been on earth for some two or three million years and

he has struggled for his life during the greater portion of the era. Thousands of years' effort by examination much has thought him to distinguishes between useful and harmful plants. Since then herbs have been used in all cultures as an important source of medicine¹. The history of human culture and civilization of Egypt,

Assyrian, China, and Indies valley, knows that the elders and wise man of those times used medicinal plants to treat many diseases. In sequence regarding these remedial plants is there in the previous text, mythological stories, folklore, medicinal treatises, epic poems and thousand years' old manuscripts, copper plates and palm leaves and other information on these cultures which are preserved even today. The unearthing of Shanidar cave in Iraq in 1963 opened the grave of a Neanderthal man buried sixty thousand years ago along with so many flowers of his time. The plants there in the severe were afterward recognized to have numerous remedial assets². Medicinal plants are the only inexpensive and reachable source of primary health care for them, particularly in the lack of access to contemporary medical facilities. Studies divulge that there are more conventional medicine providers than allopathic providers, particularly in rural areas³. Plant-resulting materials have recently befallen a huge consideration due to their adaptable appliances. Remedial plants are the wealthiest bio reserve of drugs of conformist structures of medication, food supplements, folk medicines, contemporary medicines, pharmaceutical intermediates and chemical entities for synthetic drugs⁴.

Medicinal plants form a huge group of inexpensively significant plants that provide the essential raw materials for indigenous pharmaceuticals⁵. Plant products still remain the most important source of pharmaceutical agents used in conventional medicine⁶. According to the WHO the primary step for recognition and purification of herbal drugs is the pharmacognostic (macroscopic and microscopic) studies that are necessary for any phytopharmaceutical products used for standard formulation⁷. Preliminary phytochemical studies are obliging in finding out chemical constituents in the plant material that may fine lead to their quantitative estimation^{8,9}. Lately much concentration has directed towards extracts and biologically active compounds isolated from accepted plant species. In the present age of drug development and discovery of newer drug molecules, a lot of plant products are assessed on the basis of their conventional uses. The healing properties of medicinal plants are mostly due to the occurrence of various multifaceted chemical substances of dissimilar compositions which happen as secondary metabolites¹⁰. The most significant of these bioactive constituents of plants are steroids, tannins, alkaloids, flavonoids and phenolic compounds. Therefore, it is enviable to know the phytochemical composition of the plant material before testing its effectiveness for medicinal purpose. Plants are also main natural sources of medicinal compounds in present pharmacopoeias¹¹. Indian Materia Medica comprises about 2000 drugs of natural origin and most of them are resulting from different conventional system and myths practices¹². However, there are large numbers of plants, which have not been mentioned in these reports, in malice of their usage in the conventional and folk medicinal systems. *S. marianum* common name is milk thistle; it is an edible plant belongs to the Asteraceae family. It is an annual or biennial native to the Mediterranean regions of Europe, North Africa and the Middle East and in some parts of USA¹³. In India, it is commonly found in Jammu and Kashmir¹⁴. It grows to a height of three to ten feet with an erect stem that bears large, alternating, pricklyedged leaves.

The common name, milk thistle, is derived from the milky white veins on the leaves which, when broken open, yield a milky sap. Each stem bears single, large, purple flower ending in sharp spines. The fruit portion of the plant is glossy brown or drab with spots.

The plant grows at altitude of 1800-2400m in rocky or sandy soil. The plant cherishes with flowers in monsoon season from June to August¹⁵. Four different isomers were isolated from its secondary compound silymarin (silibinin, isosilibinin, silibinin and silichristin)¹⁶. *S. marianum* is hepatoprotectant for cancer patients. Tolerant of cancer therapy may progress from using this herb; reason is that it is blood and liver toxin clearing agents¹⁷. It has strong anticancer effects against breast, tumors, ectocervical and prostate¹⁸. Against the ovarian cancer, it enhanced the effectiveness of doxorubicin and cisplatin in vitro experiment¹⁹. *S. marianum* has been used safely for children²⁰, older²¹ and pregnant women²². It is used in cholestatic, etiologies, viral, alcoholic and toxic effect removing medicines²³. The taxonomical classification of *S. marianum* consists of Domain: Eukaryota, Kingdom: Plantae, Subkingdom: Viridiplantae, Phylum: Tracheophyta, Subphylum: Euphyllophytina, Infraphylum: Radiatopses, Class: Magnoliopsida, Subclass: Asteridae, Superorder: Asterales, Order: Asterales, Family: Asteraceae, Genus: *Silybum*, Species: *Marianum*, Botanical name: *Silybum marianum*, Synonyms: *Carduus marianus* L.²⁴ The common names of the plant include blessed milk thistle, milk thistle, *cardus marianus*, marian thistle, variegated thistle, Saint Mary's thistle, Mary thistle, mediterranean milk thistle, wild artichoke, wild artichoke, Christ's crown, our lady's thistle, holy thistle, venus thistle, heal thistle, wand of god's grace, marian thistle and scotch thistle (though not to be confused with *Onopordum acanthium*)²⁵. The vernacular names of the plant are English: Blessed milk thistle; thistle; Blessed milkthistle; Holy thistle; Lady's thistle; St. Mary's thistle, **Dutch**: Mariendistel, Vrouwendistel, **Germany**: Gemeine Mariendistel; Mariendistel, **Spanish**: Cardo asnal; Cardo blanco; Cardo lechero; Cardo mariano; Cardo santo; Poma, **French**: Chardon argente; Chardon marie; Chardon Notre Dame, Artichautsauvage, **Portuguese**: cardo-leiteiro, **Italy**: Cardo di Maria; Cardo mariano, **Sweden**: mariatistel, **Netherlands**: Mariadistel, **Greek**: Silybon, **Malta**: Blessed thistle, **Romanian**: Armurariu, **Russian**: Ostropestro, Swedish: Sempertin²⁶. Therefore, in this study, the ethnopharmacological review of *S. marianum* was carried out aimed at providing a detailed précis of the botany, ethnomedicinal uses, pharmacological activities and chemical composition of the species.

Research methodology

To recognize pertinent information on the phytochemistry, botany, medicinal uses and biological activities of *S. marianum*, a review was amassed based on scientific literature from a variety of sources including Google Scholar, Science Direct, Pub Med, Scielo, Springer link, Google Patents, Web of Science, Sci Finder, Scopus, Espacenet, Bio Med Central (BMC) and Medline. The keywords employed for identification of pertinent information integrated different technical name and synonyms, ordinary English names and the stipulations: ethnobotany, medicinal uses, biological activities, ethnopharmacology, pharmacology, medicinal, Phytochemistry and therapeutic value, *S. marianum*,

milk thistle *Carduus marianus* L, ect. Further literatures were finding from books, book chapters, theses, websites and conferences.

History

The medical use of milk thistle has an extensive history. Theophrastus (c.371-287 BC), a Greek philosopher and successor to Aristotle, referred to milk thistle under the name of *Pternix*²⁷. Pliny the Elder (23-79 C.E.) and Dioscorides (40-90 C.E.) both described this plant and its uses²⁸. By the 16th century, milk thistle had become a favored medicine for hepatobiliary diseases²⁹. In 1652, Nicholas Culpeper, a preeminent English herbalist, wrote *The English Physitian*, in which he noted milk thistle to be an excellent remedy for obstructions of the liver and the spleen³⁰. Milk thistle came to the Americas with the early European colonists. At the turn of the last century, the Eclectics, a group of herbalists, were using milk thistle extracts to treat liver, spleen, kidney and menstrual disorders³¹. Medical interest in this substance waned until the 1960s, when research studies primarily in Germany, re-focused attention on milk thistle and its constituents in the treatment of acute and chronic liver disease, and as a hepatoprotective agent to prevent toxic injury to the liver²⁸.

Occurrence and distribution

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^{32, 33}. It also grows in India, China, Africa and Australia. The plant was carried to North America by European colonists during the 19th century and is now naturalized in the United States and South America, Australia, China, and Central Europe³⁴. The plant was carried to North America by European colonists during the 19th century and is now naturalized in the United States and South America. Formerly cultivated in gardens, it is found in abandoned fields, old pastures and by the roadsides and, in some parts, is considered a problematic invasive weed and a target of classic biological control efforts³⁵. It is commonly found in the provinces of Mazandaran, Gilan, West and East Azarbaijan, Kermanshah, Khuzestan, Fars and Bushehr³⁶.

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 conditions³⁷, because it is hardy and adaptable³⁸. Morazzoni and Bombardelli (1995) asserted that the uppermost substance of silybin, the chief constituent of silymarin, is establish in sows from subtropical climates and not from moderate ones, because higher temperatures seem to enhance the accumulation of that compound. Milk thistle grows well and has a good yield on different soil types³⁹⁻⁴¹. Milk thistle is normally considered to be a weed that grows along roadsides and on wastelands⁴² and reported as being a noxious weed in several countries because it competes with crops both for water and for nutrients⁴³. Milk thistle proliferates best in nitrogen-rich media such as dairy yards, chicken coop waste, garbage dumps and abandoned agricultural fields⁴⁰. 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^{36, 40}. Milk thistle is a nitrate

accumulator and can be lethal when livestock ingests the plant, particularly in the early wilting stage⁴⁴.

Growing period

Milk thistle grows as a winter annual or biennial herb, depending on climate. Germination occurs in autumn and spring³⁴. Studies have shown that milk thistle seed germination is affected by light and temperature conditions⁴². Fresh milk thistle seeds seem to need an after-ripening period and germinate better at low temperatures compared 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 period⁴⁵. Melnikova (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°C⁴⁵. Ghavami and Ramin (2007) reported that the percentage of germination at 15°C was higher than in 25 and 35°C⁴⁶. After the 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 a thesis occurs 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 the 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 stages³⁴. 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 capitulum⁴⁷. A single seed head can produce around 100-190 seeds. Flavonolignan accumulation in seeds depends on the stage of flower development and is maximum at the late flowering time⁴¹.

Morphology

S. marianum is an annual or biennial tubby, a rigid herb that is also wide and jagged. Unwieldy badge basal leaves produce up in its primary period, which reclines shut to the ground. It rises to a height of 2.5 meters and a width of 0.9 meters. Each plant produces up to four stems which are hollow, spherical and be full of milky white sap. It has big leaves that are wide and glossy green. They are distinct with white vein like marking, having spiny boundaries.

The grown-up leaves have deeper lobes with a wavier margin, while the young leaves are shallowly lobed with spin. The flowers of *S. marianum* are blue or white in color, thistle like and single. They have many tubular florets that are about 6 cm in diameter and are bordered by rigid bracts that end in sharp spines. After flowering, white, thick feathery thistledown develops and spreads the seeds. Seeds are obliquely obovoid and are 6-7 millimeters long and 3 millimeters wide. The color of the seeds is brown and has a yellowish extrapolative enlarged ring at its tip and a canalculated hilum at other end². In general, two types of *S. marianum* occur in some areas of Asia including purple flowers and white flowers. Single capitalism can produce up to 200 florets with color ranging from magenta to purple. In slash from corner to corner, the fruit demonstrates a thin, chocolate external region and 2 big, opaque, white oily cotyledons. Too the fruits are an

elaiosome, plump arrangement on fruit that is wealthy in lipid and is gorgeous to ants and thus aids seeds dispersion. 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 vigor. Seeds in the secondary flower heads had a

conspicuously lower weight, when compared to the primary ones. 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 bloom⁴⁸.

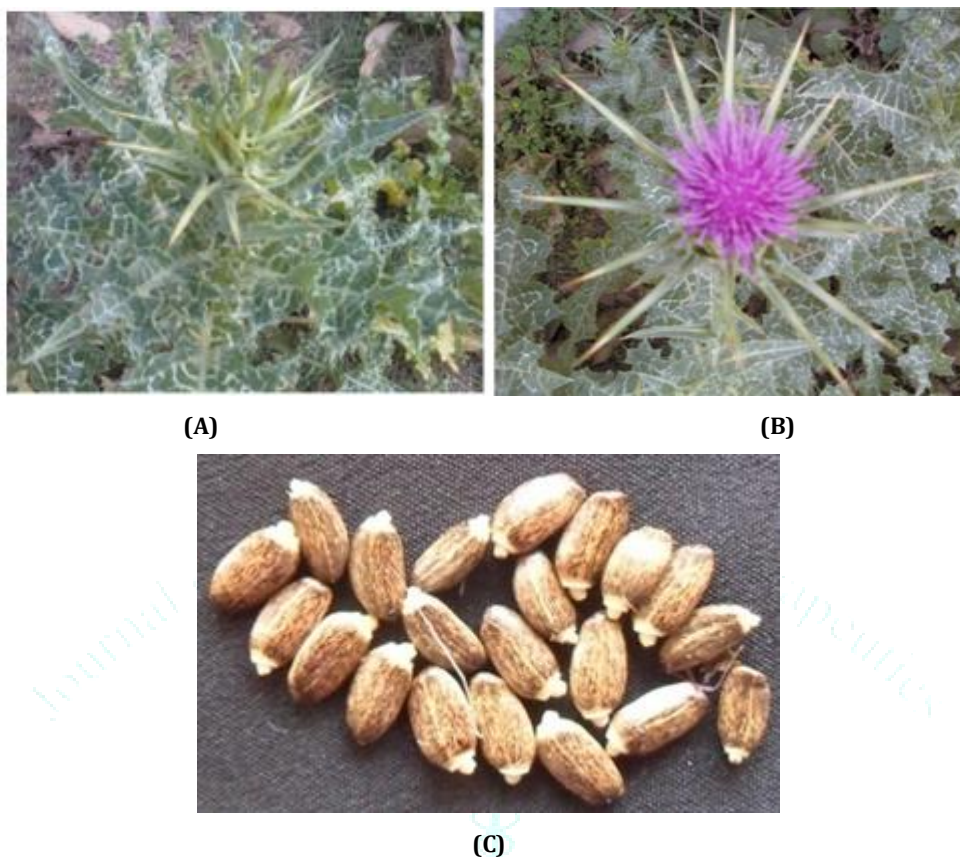


Figure 1 *Silybum marianum* (A) Plant (B) Flower (C) Seeds

Microscopy

Pericarp epidermis a colourless palisade layer of cells (about 75 μ m long and 8 μ m wide) with a strongly thickened outside wall, which reduces the lumen in that part of the cell to a slit; sub-epidermal layer composed of colourless, thin-walled, parenchyma cells or groups of parenchyma cells alternating with a variable number of pigmented cells; innermost layer mostly collapsed and containing cigar-shaped or monoclinic prismatic crystals of calcium oxalate. Testa epidermis consists of large, lemon-yellow, palisadelike, elongated cells (about 150 μ m long) with striated walls and narrow lumen widening slightly at the ends; sub-epidermal layers have lignified and pitted cells^{49,50}.

Phytochemical constituents

The first identified component of the flavonolignan complex of milk thistle, silybin (synonyms: silybinin, silibinin) including silybin A and silybin B was isolated and established by Pelter^{51,52}; Silydianin (synonym: silidianin); Silychristin (synonym: silicristin and later renamed as silychristin A; Isosilybin A and Isosilybin B; Isosilychristin; 3-deoxyflavonolignans, silandrin and silymonin; Silyhermin, neosilyhermine A and neosilyhermine B; 2,3-dehydrosilybin; 2,3-cis-silybin A, 2,3-cis-silybin B and neusilychristin; Isosilandrin A and isosilandrin B⁵³ (Samu et al., 2004); Silychristin B, a

diastereomer of silychristin A; Silyamadin; Isosilybin C and Isosilybin D. Mariamides A and B, 4-hydroxy-N-benzamide, 4-hydroxy-N--benzamide, N,N-1,4-butanediylbis (4-hydroxy-benzamide), 4,4'-diphenylmethanebis (methyl) carbamates, taxifolin, dihydrokaempferol, dihydroquercetin-4'-methylether, naringenin, naringenin 7-O- β -D-glucopyranosid, kaempferol, coniferin, 3-methylcarboxymethyl-indole-1-N- β -D-glucopyranoside, and dehydrodiconiferyl alcohol-4- β -D-glucoside; donepezil, rutin, quercetin and morin; Taxifolin; (1R, 7R, 10R, 11R)-12-hydroxyl anhuienosol; 2-hydroxymethyl-5-(2-hydroxypropan-2-yl)phenol; 2-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)phenyl β -D-glucopyranoside, (R)-2-(3-hydroxyl-4-methylphenyl) propan-1-ol; Chlorogenic acid and caffeic acid⁵⁴.

Traditional uses

In Europe, milk thistle is used in jaundice and other biliary affections. As a diet or in infusion it is said to be a reliable galactagogue. Silymarin is frequently used as helpful treatment in foodstuff toxic owing to fungus. **Root:** Root is eaten boiled as a potherb. **Herb:** Herb is used for intermittent fevers, dropsy & uterine troubles. A decoction of it is said to be beneficial as an external application in cancer. **Leaves:** Leaves are sudorific and

aperient. Juvenile leaves dish up as salad and blossoming skulls are inspired by diabetics. **Seeds:** Seeds are pungent, demulcent and antispasmodic. They are used for the treatment of jaundice and calculi of liver and gall-bladder and are useful in controlling hemorrhages.

Alcoholic extracts of the seed and to a lesser extent of the plant **together**, increase the peristalsis of the small intestine and galenical preparations, both of the seed and oil are mild purgative. Seeds are used as a substitute for coffee⁵⁵. Its flowers, leaves, and roots have been used as European diets as a vegetable, and its achene is used as a coffee. It considered a spinach substitute. The flower head is used for medicine. It is used as a remedy for Amanita mushroom toxins⁵⁶.

Mechanisms of action

Silymarin's hepatoprotective effects are accomplished via several mechanisms including antioxidation, inhibition of lipid peroxidation and enhanced liver detoxification via inhibition of Phase I detoxification and enhanced glucuronidation and protection of glutathione depletion.

Reading have also revealed silymarin displays numerous anti-inflammatory property, including inhibition of leukotriene and prostaglandin synthesis, Kupffer cell inhibition, mast cell stabilization, and inhibition of neutrophil migration. In addition, silymarin has been shown to increase hepatocyte protein synthesis,

thereby promoting hepatic tissue regeneration. Animal studies have also demonstrated silybin reduces the conversion of hepatic stellate cells into myofibroblasts, slowing or even reversing fibrosis. Clinical studies conducted in Hungary also demonstrated silymarin to have immunomodulatory effects on the diseased liver⁵⁷.

Pharmacokinetic

Not solubility in water of Silymarin, making tea preparations ineffective; therefore it is usually administered orally in encapsulated form. Since incorporation of silymarin from the GIT is only temperate (23-47%), it is best administered as a standardized extract of 70-80 percent silymarin. In animals and humans, peak plasma levels are reached in four to six hours after an oral dose. Silymarin is excreted primarily via the bile but some clearance is also achieved via the kidneys. The clearance half-life of silymarin is six to eight hours^{58,59}.

Dosage/toxicity

S. marianum is typically given as a homogeneous extract (70-80% silymarin) in encapsulated form, 100-300mg 3 times every day being the characteristic adult dose. Both animal and human studies have shown silymarin to be non-toxic. At high doses (>1500 mg per day) a laxative effect is possible due to increased bile secretion and flow. Mild allergic reactions have also been noted but were not serious.

Reported pharmacological activities of *S. marianum*

Activity	References
Antioxidant activity	Admah et al 2013 ⁶⁰ , Lucini et al 2016 ⁶¹ , Qin et al 2017a ⁶² , Nazir et al 2018 ⁶³ ,
Inflammatory effects	Qin et al 2017b ⁶⁴
Antiviral activities	Das et al 2008 ⁶⁵ , Cardile et al 2017 ⁶⁶
Antidiabetic activities	Maghrani et al 2004 ⁶⁷ , Qin et al 2017c ⁶⁸ , Derosa et al 2016 ⁶⁹ , Ebrahimpour-Koujan et al 2015 ⁷⁰ , Ebrahimpour-Koujan et al 2018 ⁷¹
Anti-amnesia effects	Nazir et al 2018 ⁶³ ,
Cardio-protection	Vilahur et al 2018 ⁷² , Ulas et al 2013 ⁷³ , Erel 2004 ⁷⁴ , 2005 ⁷⁵
Hepatic protection	Shaker et al 2010 ⁷⁶ , Aghazadeh et al 2011 ⁷⁷ , Zhu et al 2018 ⁷⁸ , Albassam 2017 ⁷⁹ , Doehmer 2011 ⁸⁰
Wilson's disease	Jedlinszki et al 2016 ⁸¹
Obsessive-Compulsive Disorder	Sayyah et al 2010 ⁸²
Sepsis and Burn prevents	Toklu et al 2007 ⁸³ , 2008 ⁸⁴
Application on veterinary	Cullere et al 2016 ⁸⁵ , Kosina et al 2017 ⁸⁶
Hypocholesterolaemic Activity	Skottova and Krecman 1998 ⁸⁷
Anti-hypertensive Activity	Jadhav et al 2011 ⁸⁸
Neuroprotective Activity	Kittur et al 2002 ⁸⁹
Anti-cancer Activity	Bhatia et al 1999 ⁹⁰
Anti-aflatoxin activities	Alhidary et al 2017 ⁹¹
Antidote activity	Fanoudi et al 2018 ⁹²

Conclusion

S. marianum is one of the most important medicinal plants grown in the world. This article reviews the phytochemistry, pharmacological, therapeutic applications and traditional knowledge of the plant *S. marianum*. The plant had been extensively used as a medicinal and legendary plant for a long period of time. *S. marianum* has attracted substantial attention due to its outstanding benefits. Pharmacological investigation on flavonolignans have been carry out *in vitro* and also urbanized *in vivo* in animal models and human experiments. Though several pharmacological mechanisms related to

biological activity have already been explained, the comprehensive pharmacological mechanisms of the *S. marianum* need to be elucidated. Based on phytochemical and pharmacological research, the silymarins responsible for the good anti-diabetic, anti-amnesia, hepatic-protective activities were selected as chemical markers to evaluate the quality of the *S. marianum* and its products.

Though, pharmacokinetics investigations on the chief constituents, particularly the bioactive constituents are silent mainly absent, so unyielding confirmation for more scientific claim is essential in regulate to review the therapeutic

potential of the *S. marianum* and its pharmaceutical commodities such as cardio-protection activity.

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