



MILK THISTLE (*SILYBUM MARIANUM*) : REVIEW ON ITS MORPHOLOGY, CHEMISTRY & PHARMACOLOGICAL ACTIVITY

¹Sujit Chavan, ²Pravin Badhe

¹Student, ²Assistant Professor

^{1,2}Pharmacology

^{1,2}Sinhgad College of Pharmacy, Vadgaon BK, Pune 411001, India

²Founder Swalife Biotech Ltd Ireland Europe

Abstract : India has a long history of employing a variety of plants medicinally. Remediation plants are working together in a very active position in conventional medications for the treatment of various illnesses. Yet, the lack of documentation and strict quality control methods has been a major barrier to the promotion of alternative medicine use in wealthy nations. There is an interest in the results of every investigation of conventional treatments that appears to be certification. This review's objective is to provide current information on the botany, morphology, phytochemistry, and pharmacological activity of various *Silybum marianum*. The technical literature for this review was compiled utilising databases like Google scholar, etc. The tall herb *S. marianum*, which belongs to the Asteraceae family, has broad, prickly white-veined green leaves and a reddish-purple bloom with sharp spines at the terminal. Milk thistle is now common in Central Europe, Central Asia, and South Australia, Western Asia, North Africa, North and South America. Confident chemical constituents were exposed cognate as silybin A, silybin B, isosilybin A, isosilybin B, silychristin, silydianin, kaempferol, taxifolin and quercetin. The plant is only used as an antioxidant, anti-inflammatory, anti-cancer, hepatoprotective agent.

keywords: *Silybum marianum*, Asteraceae, Phytochemistry, Pharmacological

INTRODUCTION

There are numerous uses for plants, Natural products have a long history that may be traced back to the dawn of human consciousness. It is estimated that cultured and civilised man has been on the planet for two to three million years, and for the most of that time, he has struggled for survival. He has spent thousands of years studying plants in order to discern between those that are beneficial and those that are harmful. Since then, all societies have employed plants as a significant source of medicine [1]. Elders and wise men in ancient Assyria, China, and the Indies Valley are aware that they employed medicinal plants to several diseases with. The previous section lists mythological tales, folklore, medical treaties, epic poems, manuscripts dating back thousands of years, copper plates, and palm leaves in order to provide information on these cultures that is still current. The corpse of a Neanderthal man who was buried with several flowers from his era was discovered in the Shanidar cave in Iraq in 1963. It was later discovered that the plants there in the harsh have many restorative resources [2]. They have little access to modern medical facilities, therefore medicinal herbs are their only affordable and practical source of basic healthcare. Studies show that conventional medicine practitioners outnumber allopathic practitioners, especially in rural areas [3]. Plant-derived materials have recently gained a lot of attention because of their adaptive features. The richest bioreservoir of pharmacological intermediates, food supplements, traditional remedies, modern medications, and chemical entities for synthesised drugs is comprised of remedial plants[4]. The milky white veins on the leaves gave rise to the common name "milk thistle," which when ripped apart, releases a milky sap. A solitary, sizable purple blossom with sharp spines grows on each stem. The plant's fruit is shiny brown or dull with markings. The plant thrives in rocky or sandy soil at a height of 1800–2400 m. The plant blooms from June to August 15 during the monsoon season. From its secondary product silymarin, four distinct isomers (silydianin, isosilybinin, silybinin, and silychristin) were isolated [5]. Hepatoprotective agents for cancer patients include *S. marianum*. Because it is a blood and liver toxin clearing agent [6], utilising this herb may improve the tolerability of cancer therapy. Against breast, malignancies, ectocervical, and prostate cancers, it exhibits potent anticancer properties [7]. It improved the efficacy of doxorubicin and cisplatin in an in vitro experiment against ovarian cancer [8]. *S. marianum* has been used without incident by older people, pregnant women, and children [9,10]. It is utilised in medications for cholestatic, viral, alcoholic, and toxic impact removal [11].

RESEARCH METHODOLOGY

A review was compiled based on available data to identify pertinent facts regarding the phytochemistry, botany, pharmacological activities of *Silybum marianum*. On scientific literature obtained from sources, such as Google Scholar & keywords used such as morphology, Chemical constituents, pharmacological activity of milk thistle.

HISTORY

Since the days of ancient physicians and botanists, milk thistle has been used to treat an array of ailments. Hepatitis, cirrhosis, and jaundice are examples of the extent of liver and gallbladder obstructions. Wind nibbles are an example of a natural poison that can injure the liver. alcohol, harmful mushrooms, and bug stings. The history of milk thistle begins with its name. The scientific name for milk thistle is *Silybum marianum*; "marianum" derives from the myth that the white veins in the plant's leaves were brought on by a drop of the virgin mary's milk [13,14,15,16]. *Silybum* is the name Dioscorides gave to all thistles. As Mary was searching for a location to care for the infant Jesus while travelling to Egypt, she was only able to discover a shield in a bower made of the milk thistle's spiky leaves [12]. The folklore that the plant was beneficial for nursing mothers originated from this tale [17]. The aster or daisy family (Asteraceae), which also includes a variety of other thistles and the artichoke, may include milk thistles as members [18]. One of the most important medicinal plants in this genus is milk thistle [19]. Every part of the plant, from the root to the hull, has been used in some capacity for ages [16,17]. The milk thistle can be consumed in a number different ways, according to Maud Grieve, including the leaves as a salad, the crude stalks (which are regarded as pleasing and nourishing), and the heads as an artichoke [19]. Bryant, who stated in his *Vegetation Dietetica* that "the young shoots in the spring, cut near the root with section of the stalk on, is one of the nicest boiling dishes of mixed greens that's eaten, and surpasses the finest cabbage," is another source that she used. Like salsify roots, the roots can be consumed [19]. Moreover, milk thistle has unquestionably been used as animal food. Grieve wrote that because pigs favoured the leaves, they are known as "pig leaves" in some parts of England. Moreover, goldfinches like to eat the seeds [19]. Before the introduction of spatial green crops, the leaves were widely used in Scotland as a source of nutrition for cattle and horses (the leaves were beaten and smashed to remove the prickles). Barbed wire has actually been replaced by milk thistle prickles in some instances [20].

After Adam and Eve were ejected from the Garden of Eden, God warned them in this phrase that "thorns likewise and thistles should it bring forward to there. Ancient Greek and Roman physicians and herbalists, each of whom appeared to have their own name for the herb, were some of the most punctilious individuals to use and write about milk thistle. Theophrastus referred to it as "pternix," Dioscorides termed it "silybon," and Pliny the Elder dubbed it "sillybum". Putting it in a tea was advised by Dioscorides "for those that be chomped of serpents" [12].

Pliny the Senior, a renowned ancient botanist, wrote that mixing nectar and plant juice was excellent for "carrying off bile" [13, 20].

A few texts from the mediaeval ages mention milk thistle, the most notable of which being an old Saxon remedy list, which claimed that "this wort if hanging upon aman's neck it setteth snakes to flight" [19]. John Gerard (1545–1612), one of the greatest renowned botanists of his day, suggested using milk thistle to treat melancholy and diseases that are associated to it [12,19,20,]

Table:1 The taxonomical classification of *S. marianum*

Domain	Eukaryota
Kingdom	Plantae
Subkingdom	Viridiaeplantae
Phylum	Tracheophyta
Subphylum	Euphyllophytina
Infraphylum	Radiatopses
Class	Magnoliopsida
Subclass	Asteridae
Superorder	Asteranae
Order	Asterales
Family	Asteraceae
Genus	<i>Silybum</i>
Species	<i>Marianum</i>

Botanical name: *Silybum marianum*

Synonyms: *Carduus marianus* L [21,22].

The popular names for The plant is known by a number of common names, including 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 [23,24].

OCCURRENCE AND DISTRIBUTION

Originally from the Mediterranean, milk thistle is now common in Central Europe, Central Asia, and South Australia, Western Asia, North Africa, North and South America [25,26]. Additionally, it flourishes in Australia, China, Africa, and India. During the 19th century, European colonists brought the plant to North America, and it is now native to South America, Australia, China, and Central Europe [27,28,29].

The plant was brought to North America by European settlers in the 19th century, and it has now become a native of both South and North America. It was once grown in gardens and is now found in unused land, old pastures, and by the sides of roads. In some regions, it is regarded as a troublesome invasive weed that must be controlled using traditional biological methods [30]. The provinces of Mazandaran, Gilan, West and East Azarbaijan, Kermanshah, Khuzestan, Fars, and Bushehr are frequent locations for it [31].

MORPHOLOGY

The five to ten-foot-tall milk thistle is a tall biennial herb with stiff, shiny, green leaves that have prickly edges and white veins running through them. The bracts on the single, reddish-purple flower heads have sharp spines at their tips. Technically known as achenes, the little hard fruit in the flowers that resembles seeds is a component of a plant that is utilised medicinally. South and Western Europe, South America, and Eastern USA and California in North America are all places where milk thistle is grown. 1-4% of Silymarin's flavonoids can be found in dried seeds.



Fig.1 *Silybum marianum*[32]

Stem :-

Description colour and texture- Stout, rigid, glabrous or slightly downy and not spiny, Branched or unbranched.

Dimensions- 3m, 40-200cm, 200-250cm.

Leaf :-

Description colour and texture- Alternate, glossy, dark green with milk white veins running throughout, **Basal leaves:** alternate, large, deeply lobed and glabrous with spiny margins, **Stem leaves:** alternate and smaller, clasp the stem, not quite as lobbed

Dimensions- Length: 75cm Width: up to 30cm

Root :- One long taproot

Inflorescence:-

Description colour and texture- Large and round capitula, Solitary at the apex of the stem or its branches, surrounded by thorny bracts.

Dimensions- Diameter of flower head- about 5cm.

Seed:-

Description colour and texture- Heavy flat, smooth and shiny, achene, with a white silky pappus and colour ranging from black, with a cocoa like odour and oily taste.

Dimensions- Broad:3mM thickness:1.5mm length:6-8mm Pappus scales: 15-20mm. [33,34,35,36].

CHEMICAL CONSTITUENTS:-

Traditional milk thistle extract is made from the seeds, which contain approximately 4–6% silymarin. The extract consists of about 65–80% silymarin (a flavanolignan complex) and 20–35% fatty acids, including linoleic acid[37,38].

Silymarin is a complex mixture of polyphenolic molecules, including seven closely related flavanolignans (silybin A, silybin B, isosilybin A, isosilybin B, silychristin, isosilychristin, silydianin) and one flavonoid (taxifolin). Silibinin, a semipurified fraction of silymarin, is primarily a mixture of 2 diastereoisomers, silybin A and silybin B, in a roughly 1:1 ratio[39,40,41,42]

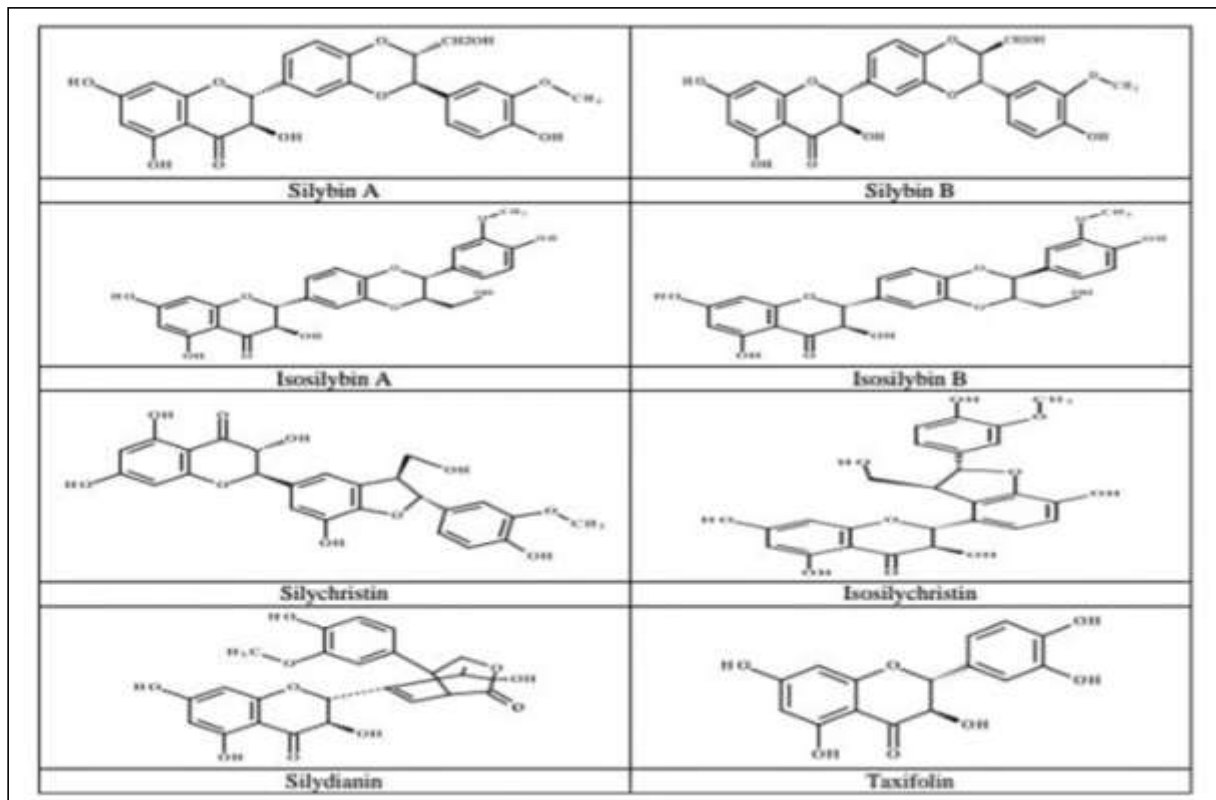


Fig.2 Chemical constituents

PHARMACOLOGICAL ACTIVITY

As a result of its diverse physiological properties, milk thistle is used for many different medical conditions. Research has established this. Silymarin, which is produced from milk thistle fruits, can help with cleansing and detoxifying as well as the regeneration of damaged cells. It can also prevent the degradation of healthy liver cells. [43, 44].

Silymarin, silybin, and other milk thistle constituents have a number of potential hepatoprotective modes of action, including anti-inflammatory, antioxidant, toxin-blocking, increased protein synthesis, and anti-fibrotic activities [45,46].

The hepatoprotective effect of *Silybum marianum* active principles has already been mentioned. The hepatoprotective effect, alcoholic liver diseases, viral hepatitis, liver cirrhosis, toxic and drug diseases of the liver, mushroom poisoning, diabetes patients with chronic liver disease, and hypocholesterolemic action were just a few of the effective pharmacological uses for milk thistle [47,48].

Antioxidant activity

In an article published recently by Nazir et al. (2018) [49], the in vitro antioxidant properties of methanol extracts from SM were assessed utilising IC₅₀ values for the DPPH and ABTS radical scavenging systems are 280 and 250 g/mL, respectively. For the return in method, a detailed comment is provided below in order to guarantee the right results. The plant sample was prepared in methanol in the concentration range of 1 mg/mL at various concentrations, and the authors used "DPPH solution prepared by taking 24 mg in 100 mL of methanol, followed by 0.1 mL of methanol extract were mixed with 3 mL of DPPH solution and incubated at 23°C for 30 min." We wanted to draw attention to the preparation of radical solutions, which might be flawed because the authors' diluted DPPH solution concentration was too high (24% w/v). It is difficult to interpret these data on the impact of methanol extracts on antioxidant capacity since we believe that this concentration is too high to create an adequate dilution and that the chemical reaction may not be complete. To help explain this position, a few common research will be included as technique references [50,51,52,53,54].

Hepatic protection

After being evaluated for 10 days against liver damage brought on by carbon tetrachloride (2 ml/kg BW), ethanol and ethyl acetate seed extracts were compared to the conventional hepatic medication hepaticum at the same dose. The liver enzymes were dramatically reduced by ethanol extract, while glutathione levels and the risk factor HDL/LDL were significantly increased by ethyl acetate. To claim more trustworthy results, we advise conducting a complete compositional study to pinpoint the active ingredients in each extract [55]. In experimental N-Mary rats with non-alcoholic steatohepatitis (NASH) brought on by the SM's ethanol extract, diets low in methionine and choline (MCD). The severity of non-alcoholic steatohepatitis in the rats receiving MCD has been reduced by administering the SM extract. Both the levels of aspartate amino transferase and alanine amino transferase dramatically decreased. Together with an increase in glutathione, the increased hepatic TNF- and TGF- mRNA levels and melondialdehyde levels also sharply dropped. Procasase-3 activation was reduced to active casepase-3 in the extract treatments, too [56]. Results from a recent study by Zhu also support this report. The findings suggested that SM oil may have some protective effects against nonalcoholic fatty liver disease, and these effects may include a reduction in lipid buildup, oxidative stress, and inflammation, as well as an improvement in lipid metabolism[57].

Anti-cancer activity

There may be a synergistic effect between milk thistle silibinin and common cytotoxic breast cancer treatments, according to an in vitro study [58]. By inhibiting the threshold kinase activities of cyclin-dependent kinases and related cyclins, milk thistle extract may exert a potent anti-carcinogenic action against breast cancer, resulting in a G1 stop in cell cycle progression [59]. On human prostate cancer, milk thistle extracts have anti-cancer properties. The anti-cancer effects of milk thistle silibinin in prostate cancer are most likely mediated via nuclear factor kappa B, insulin-like growth factor receptor type I, and epidermal growth factor receptor signalling [60]. The most potent inhibitors of prostate-specific antigen release by androgen-dependent LNCaP cells may be isosilybin A and B. Researchers hypothesised that milk thistle extracts enhanced for isosilybin A or B would have enhanced effectiveness in treating and preventing prostate cancer [61]. Lastly, 5 α -dihydrotestosterone was discovered to be downregulated by milk thistle silibinin, suggesting that milk thistle may benefit prostate [62].

Anti-inflammatory activity

Due to their remarkable antioxidant properties, which scavenge free radicals that function as pro-inflammatory agents, milk thistle seed and its active extract silymarin have anti-inflammatory and anti-arthritis benefits. In comparison to cases of established arthritis, silymarin was found to be more helpful in cases of arthritis development. By preventing neutrophil migration and suppressing Kupffer cells, silymarin and silibinin reduce inflammation. Also, by blocking the 5-lipoxygenase pathway, they prevent the production of inflammatory mediators including prostaglandins and leukotrienes as well as the basophil release of histamine. Milk thistle seed may therefore have antiallergic and anti-asthmatic properties. [63,64]

3. CONCLUSIONS

One of the most significant medicinal plants grown everywhere in the globe is *Silybum marianum*. This article examines the pharmacological, medicinal, and phytochemistry uses and conventional wisdom of the *S. marianum* plant. The plant had a long history of use as a renowned and widespread medicinal plant. *S. marianum* has received a lot of attention because of its exceptional advantages. In vitro and in vivo studies on flavonolignans have both been conducted, using both animal models and human subjects. The full pharmacological mechanisms of *Silybum marianum* remain to be clarified, even though some pharmacological mechanisms connected to biological activity have already been explained. The silymarins responsible for the good hepatic-protective actions were chosen as chemical markers to assess the quality of the *Silybum marianum* and its products based on phytochemical and pharmaceutical research. validation of more scientific claims is therefore necessary to control this review.

ACKNOWLEDGEMENT

This work was supported by the Sinhgad College of Pharmacy, Pune & Principal Dr.R.B.Patil, I would like to give heartfelt thanks to Dr.Pravin Badhe for providing Help required to carry out my work.

REFERENCES

- [1] Baquar SR. The Role of Traditional Medicine in Rural Environment, In: Traditional Medicine in Africa, Issaq, S. (Editor), East Africa Educational Publishers Ltd., Nairobi 1995, pp. 141-142.
- [2] Khan FA, Zahoor M, Ullah N, Khan S, Khurram M, Khan S, Ali J. A general introduction to medicinal plants and silybum marianum. Life Science Journal 2014; 11(9s): 471-481.
- [3] World Health Organization. Containing Antimicrobial Resistance: Review of the Literature and Report of a WHO Workshop on the Development of a Global Strategy for the Containment of Antimicrobial Resistance. WHO/CDS/CSR/DRS/99.2; 1999.
- [4] Ncube NS, Afolayan AJ, Okoh AI, Assessment techniques of antimicrobial properties of natural compounds of plant origin: current methods and future trends, African Journal of Biotechnology 2008; 7: 1797-1806.
- [5] Lee DY, Liu Y. Molecular structure and stereochemistry of silybin A, silybin B, isosilybin A and isosilybin B, isolated from *Silybum marianum* (milk thistle). J Nat Prod 2003; 66: 1171- 1174.
- [6] Ladas EJ, Cheng B, Hughes D. Milk thistle (*Silybum marianum*) is associated with reductions in liver function tests (LFTs) in children undergoing therapy for acute lymphoblastic leukemia (ALL). Society of Integrative Oncology, Boston, Mass 2006.
- [7] Bhatia N, Zhao J, Wolf DM. Inhibition of human carcinoma cell growth and DNA synthesis by silibinin, an active constituent of milk thistle: comparison with silymarin. Cancer Lett 1999; 147: 77-84.
- [8] Duthie SJ, Johnson W, Dobson VL. The effect of dietary flavonoids on DNA damage (strand breaks and oxidised pyrimidines) and growth in human cells. Mutat Res 1997; 390: 141-151.
- [9] Allain H, Schück S, Lebreton S. Aminotransferase levels and silymarin in de novo tacrine-treated patients with Alzheimer's disease. Dementia Geriatr Cogn Disord 1999; 10: 181-185.
- [10] Greenlee H, Abascal K, Yarnell E, Ladas E. Clinical applications of *Silybum marianum* in oncology. Integr Cancer Ther 2007; 6: 158-165.
- [11] Eliss RH, Covell S, Roberts EH, Sumerfield RG. The influence of temperature on seed germination rate in grain legumes. II. Interspecific variation in chickpea (*Cicer arietinum* L.) at temperature. J Exp Bot 1986;37: 1503-1515.
- [12] WHO monograph of selected medicinal plants. 1999;300-316 (March).
- [13] Brown D. Silymarin education monograph. Herbal Res Update 1993; Summer:23-36.
- [14] Gaertn SL. Milk Thistle AND. 2000;285-95.
- [15] Luper S. A Review of Plants Used in the Treatment of Liver Disease : Part 1. 1998;3(6):410-21.
- [16] Grove P. MILK THISTLE. 1995;1-27.
- [17] ZONOUBI, Ahmad, et al. Milk thistle-morphology, chemistry and pharmacological action. *INTERNATIONAL JOURNAL OF INNOVATIVE PHARMACEUTICAL SCIENCES AND RESEARCH*, 2019, 7.2: 14-40.
- [18] Hobbs C. Milk thistle: The liver herb. Loveland (CO): Interweave Press; 1994.

- [19] Grieve M. A modern herbal: The medicinal, culinary, cosmetic and economic properties, cultivation, and folklore of herbs, grasses, fungi, shrubs, and trees with all their modern scientific uses. Darien (CT): Hafner Publishing Company; 1931.
- [20] Flora K, Hahn M, Rosen H, et al. Milk thistle (*Silybum marianum*) for the therapy of liver disease. *Am J Gastroenterol* 1998; 93:139-43.
- [21] http://www.zipcodezoo.com/Plants/S/Sylibum_marianum.
- [22] SMITH, W. A., LAUREN, D. R., BURGESS, E. J., PERRY, N. B., MARTIN, R. J. (2005). A silychristin isomer and variation of flavonolignan levels in milk thistle (*Silybum marianum*) fruits. *Planta medica*, 71(09), 877-880
- [23] Patel CJ, Tyagi S, Kumar U, Patel S, Patel Ph, Bharat C. Clinical benefits of milk thistle (*silybum marianum*): a recent review. *Journal of Drug Discovery and Therapeutics* 2013; 1 (1): 08-11
- [24] Adetuyi, Babatunde O., et al. "Pharmacological, biochemical and therapeutic potential of milk thistle (silymarin): a review." *World News of Natural Sciences* 37 (2021): 75-91.
- [25] Libster M. *Delmar's integrative herb guide for nurses*. Thomson Learning. 2002, pp: 669 -77.
- [26] British Pharmacopoeia. *Herbal Drugs and Herbal Drug Preparations Milk-thistle Fruit*. 2009, Volume III. pp: 7173.
- [27] Das SK, Mukherjee S and Vasudevan DM. Medicinal properties of milk thistle with special reference to silymarin an overview. *Natural Product Radiance* 2008; 7 (2): 182- 92.
- [28] CARRIER, D. J., CROWE, T., SOKHANSANJ, S., WAHAB, J., BARL, B. (2003). Milk thistle, *Silybum marianum* (L.) Gaertn., flower head development and associated marker compound profile. *Journal of herbs, spices & medicinal plants*, 10(1), 65-74.
- [29] BHATTACHARYA, S. (2011). Phytotherapeutic properties of milk thistle seeds: An overview. *Journal of Advanced Pharmacy Education & Research*, 1, 69-79. BIJAK, M. (2017). Silybin, a major bioactive component of milk thistle (*Silybum marianum* L. Gaertn.)—Chemistry, bioavailability, and metabolism. *Molecules*, 22(11),
- [30] Groves RH, Kaye PE *Aust J Bot* 1989; 37:351
- [31] Ghahreman A. *Flora of IRAN*. Research Institute of Forests Rangelands, Iran, 1999; pp: 587
- [32] HABÁN, M., GRANČAI, D., LUŠČÁKOVÁ, D. (2015). Interesting and less well-known herbal drugs in the Pharmacopoeia and Pharmaceutical Codex (7). *Liečivé rastliny*, 52(1), 29–30.
- [33] WHO monograph of selected medicinal plants. 1999;300-316 (March).
- [34] Qavami N, NaghdiBadi H, Labbafi MR, Mehrafarin A. A Review on Pharmacological, Cultivation and Biotechnology Aspects of Milk Thistle (*Silybum marianum* (L.) Gaertn.). *Journal of Medicinal Plants*, 2013; 12(47): 19-37.
- [35] Shah, Megha S., et al. "A systemic phytopharmacological review of multipotential medicinal plant milk thistle." *World Journal of Pharmaceutical Research* 9.8 (2020): 468-484.
- [36] Zonoubi, Ahmad, et al. "Milk thistle-morphology, chemistry and pharmacological action." *INTERNATIONAL JOURNAL OF INNOVATIVE PHARMACEUTICAL SCIENCES AND RESEARCH* 7.2 (2019): 14-40.
- [37] Kaur, A. K., Wahi, A. K., Brijesh, K., Bhandari, A., & Prasad, N. (2011). Milk thistle (*Silybum marianum*): A review. *IJPRD*, 3, 1-10.
- [38] Kurkin, V.A., Zapesochnaya, G.G., Volotsueva, A.V... *et al.* Flavolignans of *Silybum marianum* Fruit. *Chemistry of Natural Compounds* 37, 315–317 (2001).
- [39] Wang, X., Zhang, Z., & Wu, S. C. (2020). Health benefits of *Silybum marianum*: Phytochemistry, pharmacology, and applications. *Journal of Agricultural and Food Chemistry*, 68(42), 11644-11664.
- [40] ABENAVOLI, L., CAPASSO, R., MILIC, N., CAPASSO, F. (2010). Milk thistle in liver diseases: past, present, future. *Phytotherapy Research*, 24(10), 1423- 1432
- [41] ALBASSAM, A. A., FRYE, R. F., MARKOWITZ, J. S. (2017). The effect of milk thistle (*Silybum marianum*) and its main flavonolignans on CYP2C8 enzyme activity in human liver microsomes. *Chemico-biological interactions*, 271, 24-29.
- [42] ABOUZID, S. F., CHEN, S. N., PAULI, G. F. (2016). Silymarin content in *Silybum marianum* populations growing in Egypt. *Industrial crops and products*, 83, 729-737.
- [43] Abenavoli L, Spagnuolo R, Luppino I and Luzzza F. *Recent Progress in Medicinal Plants*. Splic Press. 2010, pp: 387 – 409.
- [44] Davis-Searles PR, Nakanishi Y, Kim N, Graf TN, Oberlies NH, Wani MC, Wall ME, Agarwal R and Kroll DJ. Milk Thistle and Prostate Cancer: Differential Effects of Pure Flavonolignans from *Silybum marianum* on Antiproliferative end Points in Human Prostate Carcinoma Cells. *Cancer Res*. 2005; 65 (10): 4448 - 57.
- [45] Johann S, Scaler F, Sonnenbichler I and Weyhenmeyerr. Stimulatory Effects of Silibinin and Silicristin from the Milk Thistle *Silybum marianum* on Kidney Cells. *JPET*. 1999; 290 (3): 1375 – 83.
- [46] Ball KR and Kowdley KV. A review of *Silybum marianum* (Milk Thistle) as a Treatment for alcoholic liver disease. *Journal of Clinical Gastroenterol*. 2005; 39 (6): 520 - 8.
- [47] Fallah Huseini H, Alavian SM, Toliat T, Jamshidi AH, Heshmat R, Naghdi Badi H and Khani M. The efficacy of herbal medicine khar maryam (*Silybum marianum* (L.) Gaertn.) on liver cirrhosis in chronic hepatitis B patients. *J. Medicinal Plants* 1994; 8: 1 - 6.
- [48] Kiruthiga PV, Shafreen RB, Pandian SK, Devi KP. Silymarin protection against major reactive oxygen species released by environmental toxins: exogenous H₂O₂ exposure in erythrocytes. *Basic Clin. Pharmacol. Toxicol*. 2007; 100: 414 – 9.
- [49] Nazir N, Karim N, Abdel-Halim H, Khan I, Wadood SF, Nisar M. Phytochemical analysis, molecular docking and anti-amnesic effects of methanolic extract of *Silybum marianum* (L.) Gaertn seeds in scopolamine induced memory impairment in mice. *Journal of ethnopharmacology*. 2018; 210:198-208.
- [50] Salla S, Sunkara R, Ogutu S, Walker LT, Verghese M. Antioxidant activity of papaya seed extracts against H₂O₂ induced oxidative stress in HepG2 cells. *TWTFood Science and Technology*. 2016; 66:293-297.
- [51] Cho KM, Ha TJ, Lee YB, Seo WD, Kim JY, Ryu HW, et al. Soluble phenolics and antioxidant properties of soybean (*Glycine max* L.) cultivars with varying seed coat colours. *Journal of Functional foods*. 2013; 5:1065- 1076.
- [52] Vieira PAF, Gontijo DC, Vieira B, Fontes EAF, Assuncao LSD, Leite JPV et al. Antioxidant activities, total phenolics and metal contents in *Pleurotus ostreatus* mushrooms enriched with iron, zinc or lithium. *TWLfood science and technology*. 2013; 54:421-425.

- [53] Adefegha SA, Oboh G, Molehin OR, Saliu JA, Athayde ML, Boligon AA. Chromatographic fingerprint analysis, acetylcholinesterase inhibitory properties and antioxidant activities of red flower rag leaf (*Crass ocephalum crepid ioides*) extract. *Journal of Food Biochemistry*. 2015; 40:109-119.
- [54] Blois MS. Antioxidant determinations by the use of a stable free radical. *Nature*. 1958; 181:1199-1200.
- [55] Shaker E, Mahmoud H, Mnaa S. Silymarin, the antioxidant component and *Silybum marianum* extracts prevent liver damage. *Food and Chemical Toxicology*. 2010; 48(3):803-806.
- [56] Aghazadeh S, Amini R, Yazdanparast R, Ghaffari SH. Anti-apoptotic and anti-inflammatory effects of *Silybum marianum* in treatment of experimental steatohepatitis. *Experimental and toxicologic pathology*. 2011; 63(6):569-574.
- [57] Zhu SY, Jiang N, Yang J, Tu J, Zhou Y, Xiao X et al. *Silybum marianum* oil attenuates hepatic steatosis and oxidative stress in high fat diet-fed mice. *Biomedicine and Pharmacotherapy*. 2018; 100:191-197.
- [58] Tyagi AK. Synergistic anti-cancer effects of silibinin [milk thistle extract] with conventional cytotoxic agents doxorubicin, cisplatin and carboplatin against human M breast carcinoma MCF-7 and MDA-MB468 cells. *Oncol Rep*. 2004 Feb; 11(2):493-9. Zi X.
- [59] Ant carcinogenic effect of a flavonoid antioxidant, silymarin [milk thistle], in human breast cancer cells MDA-MB 468: induction of G1 arrest through an increase in Cip1/p21 concomitant with a decrease in kinase activity of cyclin-dependent kinases and associated cyclins. *Clin Cancer Res*. 1998 Apr; 4(4):1055- 64.
- [60] Singh RP. A cancer chemopreventive agent silibinin [MILK THISTLE], targets mitogenic and survival signaling in prostate cancer. *Mutat Res*, 2004 Nov 2; 555(1-2):21-32.
- [61] Davis-Searles PR, Milk thistle and prostate cancer: differential effects of pure flavonolignans from *Silybum marianum* [MILK THISTLE] on ant proliferative end points in human prostate carcinoma cells. *Cancer Res*, 2005 May 15; 65(10):4448-57].
- [62] Thelen P Silibinin down-regulates prostate epithelium-derived Ets transcription factor in LNCaP prostate cancer cells. *Planta Med*, 2004 May; 70(5):397-400
- [63] Fiebrich F., Koch H. Silymarin, an inhibitor of lipoxygenase. *Experientia* 1979; 35: 150-152.
- [64] Dixit N., Baboota S., Kohli K., Ahmad S., Ali J. Silymarin: A review of pharmacological aspects and bioavailability enhancement approaches. *Indian J. Pharmacol*. 2009; 39: 172-17

