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Milk Thistle [*Silybum marianum* (L.) Gaertn.] - a Very Useful Plant for People's Health

COȘERAN Mihaela Anca[1], Emilia CONSTANTINESCU*[2], Andreea ONA[1], Simona BALAȘ[1], Marcel M. DUDA[1]
[1]University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Faculty of Agriculture, 3-5 Calea Mănăștur, 400372, Cluj-Napoca, Romania
[2]University of Craiova, Faculty of Agronomy, 19 Libertătii, 200421 Craiova, Romania
*Correspondence: emilia.constantinescu@edu.ucv.ro

Abstract: Milk thistle, a species mentioned from the time of Greek philosophers, is well known due to one of its constituents, silymarin, and used in the treatment of several liver disorders. Even though the majority of the documentary data on *Silybum marianum* focuses on its role in liver diseases, more information has recently become available regarding the herb's beneficial effects on a variety of other diseases, including protection for the kidneys, hypolipidemic and anti-atherosclerotic activities, cardiovascular protection, prevention of insulin resistance, particularly in cirrhotic patients, cancer prevention, and Alzheimer's and dementia prevention. Considering the preceding significance, in this paper, we present a synthesis of the knowledge related to the phytochemical constituents of the milk thistle fruits and their pharmaceutical activity, to the origin and spread of the species, to the systematics and cultivated varieties, as well as the influence of the environmental conditions and applied technology on the production and chemical composition of the fruits of these plants.

Keywords: fruit production and quality, phytochemical constituents, *Silybum marianum* (L.) Gaertn.

Introduction

The name of this plant has been mentioned since ancient times. Theophrastus (371-287 BC), the Greek philosopher successor to Aristotle, referred to the armorer as Pternix (Morazzoni and Bombardelli, 1995). Pliny the Elder (23-79 BC) and Dioscorides (40-90 BC) also described this plant and its beneficial uses (Luper, 1998).

Starting from the 16th century, armor became the main remedy for hepatobiliary diseases. It was used since the time of Hyeronimus Bosch (1595), becoming a real hepatobiliary medicine from the century. XVIII (Pârvu, 1991). In 1652, a prominent English botanist, Nicholas Culpeper, wrote the book "The English Physitian" in which he also noted that this plant is an excellent remedy for liver and spleen deficiencies. Zohary (1962) reported its use as a vegetable by the Bedouins of Palestine.

The plant returned to relevance in the 1960s, when studies in Germany refocused attention on it and its beneficial uses in acute and chronic liver diseases (Porwal et al., 2019).

Little known in Romania, milk thistle is a medicinal plant, which is cultivated for its extremely valuable fruits from a therapeutic point of view, which are recommended for the treatment of liver and gall bladder diseases.

The useful part of the plant is *Silybi mariani fructus*. Silymarin is extracted from their dry pericarp (Andrzejewska and Sadowska, 2008). In 2014, silymarin extracted from the fruit of *Silybum marianum* ranked sixth among the top twenty best-selling dietary supplements in the health and natural food market, and twelfth among the top forty herbal supplements in the market leading US company with sales of $16.4 million (Smith et al., 2015).

Milk thistle has become one of the most cultivated and economically viable medicinal plants in some parts of Europe, including Bulgaria (Zheljazkov et al., 2006). Studies undertaken by Houachri et al. (2017) showed that milk thistle can also be a potential source of biofuel along with *Citrullus colocynthis* and *Datura stramonium*.

It is also a melliferous species, the flowers providing bees with nectar and pollen for a long period, from June to September (Pârvu, 1991; Muntean, 2003).

Phytochemical constituents and their phytotherapeutic effects

Milk thistle seeds contain silymarin, bioflavonoids, amino acids (glycine, leucine, cysteine, tyramine), glutamic acid, fumaric acid, saponins, sterols and tocopherol. Silymarin has been known since ancient times and recommended in traditional European and Asian medicine mainly for the treatment of liver diseases (Morazzoni and Bombardelli, 1995). Silymarin is a complex of flavonolignans, which contains silybin, silychristin, silydianin and isosilybin, frequently used in the liver treatment (Morazzoni and Bombardelli, 1995).

In 2014, silymarin extracted from milk thistle seeds was ranked sixth among the top twenty best-0selling dietary supplements in the health and natural food market, and twelfth among the top forty herbal supplements in the mainstream market from the US with sales of $16.4 million (Smith et al., 2015).

Extracts from the milk thistle are used for many medical purposes, such as: antidiabetic, hepatoprotective, hypocholesterolemic, antihypertensive, antiinflammatory, anticarcinogenic and antioxidant. It can also be antispasmodic, neuroprotective, antiviral, cardioprotective and antihemorrhagic (Bhattacharya, 2011; Porwal et al., 2019).

Currently, the hepatoprotective activity of silymarin, based in part on its antioxidant properties, is sufficiently documented and silymarin has become an ingredient of phytopharmaceuticals (Lagalo, Flavobion) often used as a support in the therapy of mushroom poisonings affecting the liver (*Amanita* sp.) and in therapy of chronic liver diseases such as steatosis (Geller et al., 1993) and alcohol-induced diseases (Ferenci et al., 1989).

The content of silymarin in milkthistle seeds ranges between 1-3%, but can also reach 4% (Karkanis et al., 2011). The silymarin complex typically contains 36.3% silybin, 15.7% silycristin, 5.9% silydianin and 5.1% isosilybin (Sersen et al., 2006) (Figure 1, after AbouZid et al., 2016). Silybin is the component with the highest degree of biological activity and represents 50–70% of silymarin (Abenavoli and Milic, 2017). The seeds contain the most silymarin, but the whole plant is useful medicinally (Karkanis et al., 2011).

Dvorak et al. (2003), cited by Andrzejewska and Sadowska (2008), showed that, however, an effective cytoprotective effect of silydianin and silychristin, mostly, and a much less effect of silybin and isosilybin, which suggests a growing demand for raw material with a specific content of respective flavonolignans.

Milk thistle seeds also contain small amounts of flavonoids (toxifolin) and 20–35% fatty acids and polyphenolic components (Karkanis et al., 2011).

Martinelli et al. (2016) analysed the morphological and chemical traits of milk thistle fruits from a collection of 26 cultivars. The results showed that the most variable traits are related only to the content of flavonols. Oleic acid appears to have greater variability.

The lipid composition of milk thistle seeds consisting of a mixture of myristic, palmitic, stearic, oleic, linoleic and arachidonic acids showed a high degree of unsaturation (Gresta et al., 2006).

Ruzickova et al. (2011) evaluated milk thistle samples of the variety Silyb (silybin type), grown in five regions of the Czech Republic, for seed oil content and neutralization number. A second part of the study comprised six different genotypes, with evaluation of oil content, spectrum of main fatty acids, neutralization number.

Analyses showed significant differences in seed oil content depending on pedoclimatic conditions. The highest average oil content was in the warmer and less humid (cereal-growing) areas, 21.28%, and the lowest value in the cooler and more humid (potato-growing) area, 18, 97%.

Most of the documentary data on S. marianum refer to its contribution to liver diseases; however, more information has recently emerged regarding beneficial properties on a wide variety of other disorders, such as renal protection, hypolipidemic and anti-atherosclerosis activities, cardiovascular protection, prevention of insulin resistance, especially in cirrhotic patients, cancer and Alzheimer's prevention (Bahmani et al., 2015).

Origin and distribution of the species

Milk thistle it originates in the Mediterranean region and is widespread throughout Central Europe, Central and West Africa, North Africa, South America, and North America and South Australia. The plant was brought to North America by European settlers in the 19th century and naturalized in the United States and South America (Libster, 2002). This plant adapts to different climatic conditions. It can be grown in northern climates such as Canada as well as in southern and arid conditions (Wallace et al., 2008) because it is hardy and adaptable (Cwalina-Ambroziak et al., 2012). In many areas milk thistle grows along roadsides and wastelands and is considered a weed because it competes with other plants for both water and nutrients (Montemurro et al., 2007), for example in the sub-hill regions of western Punjab in Pakistan or in India, in the foothills, on the adjoining plains of Jammu and the highest areas of the Kangra Valley in the north or between the Coonoor and Ooty hills in Tamil Nadu (Kapahi et al., 1995). Even in its native environment in Israel, *S. marinum* has become a problematic weed among crops of cultivated ornamental species (Buxbaum et al., 1999).

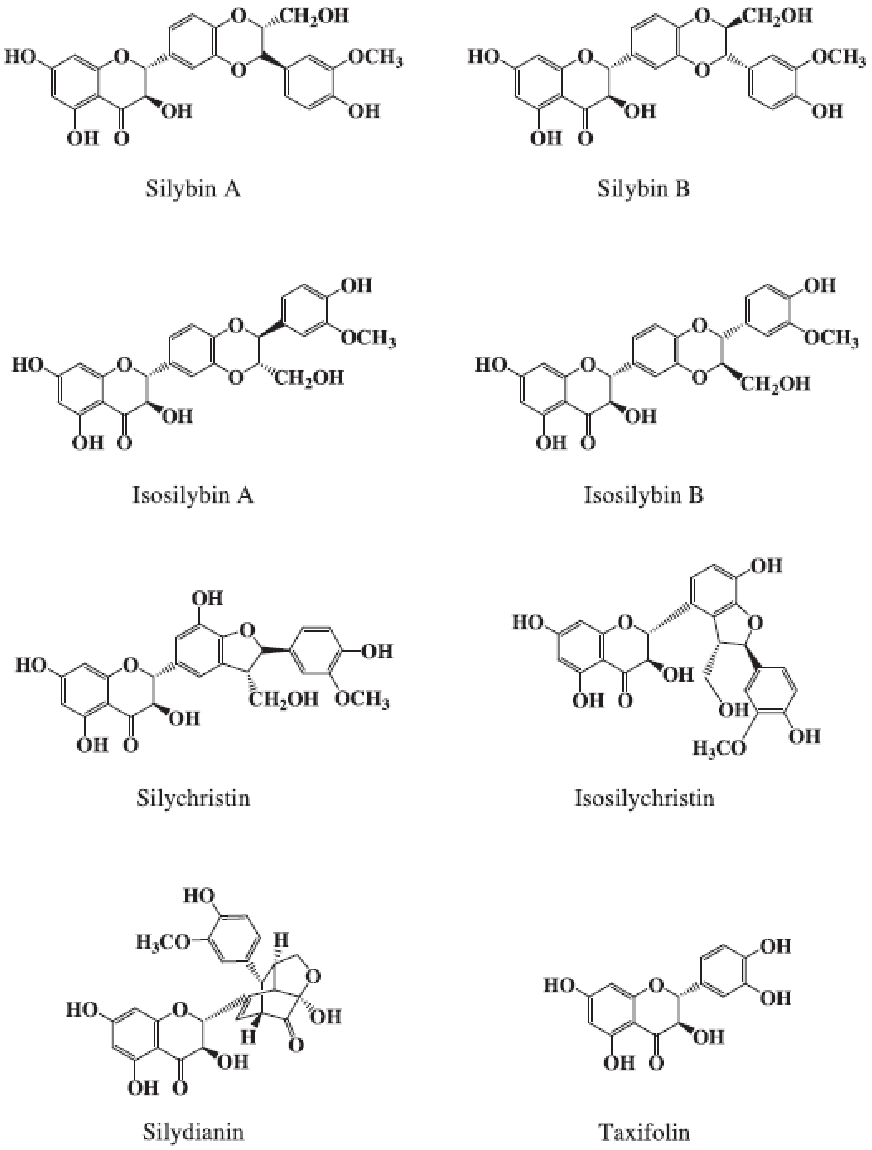

Figure 1. The components of silymarin

In habitats on the south coast of England, this species has a well-established and persistent local range, but can also be found in the depression area (https://plantatlas.brc.ac.uk).

The plant has also been reported frequently in Eastern Europe, being present in abandoned fields, old pastures and along roads. It is considered a problem weed for the control of which great efforts are made, especially by herbicides (Groves and Kaye,1989; Andrzejewska and Sadowska, 2008; Muntean et al., 2016).

In Romania, the cultivation of milk thistle is recommended in the south of Muntenia (Ialomiţa, Ilfov, Teleorman counties), the south of Oltenia (the Danube side of Olt and Dolj counties), Dobrogea, as well as in the Western Plain (Tudora, 2011).

Systematic. Varieties

In the scientific literature, the common name of this species is very diverse: blessed milk thistle, thistle, marian thistle, variegated thistle, Saint Mary’s thistle, Mary thistle, mediterranean thistle, wild artichoke, christ, crown, our lady’s thistle, blessed milk thistle, holy thistle, Mediterranean milk thistle, variegated thistle, venus thistle or Scotch thistle (Muntean și colab., 2016; wikipedia.org).

Milk thistle [*Silybum marianum* (L.) Gaertn.] (sin. *Carduus marianus*), belongs Domain Eukaryota; Regnum: Plantae; Subregnum: Viridaeplantae; Division: Tracheophyta; Subdivision: Euphyllophytina; Class: Magnoliopsida; Order: Asterales; Family: Asteraceae; Genus: *Silybum*. In terms of milk thistle improvement, the main objective is to develop cultivars (varieties) with a high content of silymarin. There are few varieties of milk thistle (example: Argintiu, Budakalaszi, Szibilla, Khoreslo, Babak Castle, Mirel, Silma and Silyb). Different milk thistle genotypes have a variable amount of silymarin, e.g. the "Royston" variety stands out for its very high content of silymarin (6-10%). The main concern of breeders should be to increase the yield and silymarin content of the seeds. Asynchronous flowering and seed shaking are also major problems in milk thistle cultivation. At the time of harvest, the plants have the capitula in all stages of development, which leads to an uneven ripening of the seeds. Therefore, it should be planned to obtain plants with simultaneous flowering and low production losses. The "Argintiu" variety is characterized by the simultaneous ripening of the seeds in the heads. Wild populations, with valuable genes, could be exploited for crop improvement (Alemardan et al., 2013).

The characterization of the phytochemical and antioxidant profiles of the achenes from fifteen different milk thistle genotypes, by measuring the total content of phenolics, flavonoids and flavonols, as well as the antioxidant capacity was the aim of the work of Lucini et al. (2016). In addition, selected individual phenolic compounds were determined by liquid chromatography tandem mass spectrometry. Most of the polyphenols in the armory were composed of chlorogenic acid and silybin. Significant differences were identified between cultivars for total antioxidant capacity and for all tested compound classes. Genotypes 1 and 2 had the highest total phenolic and flavonoid content as well as the strongest antioxidant activity. Genotype 8 contained high levels of caffeic acid, 10-15 times higher than the values obtained for the other genotypes. Antioxidant capacity was mainly correlated with total phenolics and flavonoids rather than single compounds. The study highlighted the important role of the genetic background of the armorer.

In Romania, the local population 'De Prahova' is cultivated (Druțu, 2015; ISTIS, 2022). Other varieties spread abroad are 'Argintiu' and 'Fortificator' from Republic of Moldavia (CSTSP, 2021), 'Budakalaszi Szibilla' in Hungary, 'Silma' in Poland, 'Mirel Silyb' in Czech Republic, 'Royston' in Germany, and 'Khoreslo Babak Castle' in Iran (Alemardan et al., 2013).

The effect of environmental conditions and applied technology

Due to its Mediterranean origin, the plant is demanding on temperature throughout the growing season. Armory has moderate moisture requirements, but prolonged summer drought negatively influences fruit production. The most suitable soils for this culture are those with a medium texture, deep and permeable (Druțu, 2015).

S. marianum was found to have a competitive advantage over most of its companion species, largely due to its rapid growth and biomass accumulation on soils rich in nitrogen and organic matter. Height, number of heads/plant, diameter of head, and mean number of achenes per head were significantly higher on nutrient-enriched soils (Gabay et al., 1994).

Rahimi and Kamali (2012) conducted studies on the influence of sowing date and fertilization system on seed yield and essential oil content of milk thistle seeds in Iran for 2 years. Three different sowing dates (September 1, October 15 and March 1 of the following year) constituted in large plots and 5 different fertilization systems: control (unfertilized), fertilized with N100P100; with phosphorus-based biofertilizer; only with 15 t/ha of manure and, the 5th variant, with 10 t/ha of manure + N50P50, in small plots. The delay in sowing led to a significant reduction of seeds in the inflorescence. The highest oil content (29.12%) and the highest silymarin content (2.15%) were found at the first two sowing dates in the variant fertilized with biostimulator. Silymarin content was negatively significantly and distinctly significantly correlated with oil content, 1000-grain weight, yield and harvest index.

The study of the influence of nitrogen fertilization on the growth of armor, achene production and the content of active substances (silymarin and silybin), carried out by Omidbaigi and Nobakht (2001) showed that it had a significant effect on the height, the number of heads/plant and the diameter of the head. The highest production (2.35 kg/plot) was obtained in the variant fertilized with 200 kg/ha N, but the highest contents of silymarin (9.25%) and silybin (33.58%) were accumulated in the seeds of the control variant, unfertilized. The result obtained is consistent with previous research carried out by Timmerman et al (1993), namely increasing the nitrogen dose leads to a decrease in the content of phenolic components, nitrogen acting as an inhibitor.

A study by Wierzbowska et al. (2012) examined the effect of nitrogen fertilization on biomass production and structure in two populations of milk thistle. Higher achene production and biomass were obtained in a Polish population compared to the cultivar Silma. Achene production increased proportionally with nitrogen dose. The population responded better than the cultivar to increasing nitrogen doses. The highest percentage of achenes in the total biomass was obtained by applying 2 g of N per experimental pot.

In the second experiment, the influence of boron was investigated, and in the third experiment, the impact of magnesium fertilizers (MgCl2) and (MgSO4) was studied. The achenes of the population contain significantly more phosphorus and potassium (over 1.7%) while sodium, calcium and magnesium levels do not differ significantly between the two armor forms. The highest content of nitrogen (27.62 g/kg) and phosphorus (8.78 g/kg) were obtained by applying 2 g N/experimental pot. Sulfur introduced into the soil in the form of magnesium sulfate raised nitrogen content in the achenes of both forms of armor (Wierzbowska, 2013).

Ismail et al. (2013) studied the impact of biofertilizers, organic fertilizers (cattle and poultry manure) and the combination of the two on the growth and yield of Silybum marianum. The height, number of branches, number of roots, root length and accumulated dry matter increased significantly with the application of biofertilizers in combination with an organic fertilizer. Plants treated with 10 m^3 cattle manure/plot + biofertilizer or 10 m^3 poultry manure showed significantly higher silymarin content in the second season compared to other variants tested. The data showed no protein variability in terms of the number of bands and their intensity in any variant studied.

Studies on the effect of foliar or ground fertilization and treatment with the growth regulator were deepened. Thidiazuron (TDZ) on vegetative and reproductive growth, several physiological parameters, production and silymarin content in Silybum marianum were carried out by Stanceva et al. (2008). Agroleaf was used as foliar fertilizer with 3 formulations: total with NPK 20:20:20 + microelements; Agroleaf with high phosphorus content with NPK 12:52:5 + trace elements; Agroleaf with high potassium content with NPK 15:10:31 + trace elements. The content of silymarin (2.4%), the content of silydianin + silicristin (0.95%), the content of silibinin + isosilibinin (1.45%) recorded maximum values, with statistical assurance in relation to all other variants, in the variant foliar fertilization + growth regulator. It should be noted that the next ranked variant was the control variant - without fertilization (Stanceva et al., 2008).

Hendawy et al. (2013) investigated the response of *S. marianum* plants to irrigation intervals combined with fertilization. The study was undertaken to investigate the influence of several kinds of organic fertilizers, at different irrigation rates, on growth, yield and seed chemical constituents. The data indicated that all growth and yield characters were influenced by the duration of irrigation intervals. The interaction of irrigation interval x fertilization treatments clearly had a considerable effect on growth and yield traits. The obtained results indicated a favourable effect of organic fertilizers on the harmful effect of water stress. The different treatments had a pronounced effect on the silymarin content.

Keshavarz Afshar et al., (2014), studied the response of sorghum plants to deficit irrigation and organic soil organic fertilization in a 2-year experiment with 3 levels of irrigation regimes - normal irrigation (I100), moderate (I75) and reduced (I50) - plus two sources of fertilization - vermicompost (VM) and manure (PM) plus a variant without fertilization, the plots being randomized. Moderate and severe deficit irrigation reduced seed production by 7 and 27%, respectively. Among the productivity elements, number of seeds/head showed the highest sensitivity to deficit irrigation, followed by number of heads/plant, while seed weight remained stable. Of the 2 fertilizers, only PM significantly improved seed production, with increases of 8, 12, and 17% at I100, I75, and I50, respectively. Deficit irrigation improved seed silymarin content, but silymarin yield decreased due to low seed production under water stress. Oil production was also affected under both moderate and reduced irrigation by 9 and 32%, respectively. Fertilization had no significant effect on silymarin and seed oil concentration, but PM increased seed production. The results of this study indicated that buttercup can be grown moderately irrigated (saving 25% of irrigation water) and soil fertilization with PM can improve production and minimize the negative impact of drought stress.

Over two years, Arampatzis et al (2019) evaluated the effects of plant density and a growth regulator on armor plant growth, seed production and silymarin accumulation under semiarid Mediterranean conditions. The results showed that plant density had a significant impact on plant growth and seed production. Main plant characteristics such as height, aboveground biomass and seed production were greatest when plant density was highest. Increased plant density significantly reduced silymarin content only in 2018. In contrast, mepiquat chloride (MC) treatment did not affect plant biomass, relative chlorophyll content, silymarin content and yield. However, MC reduced plant height by 7.9–14.8%, depending on application rates and growth conditions. Moreover, the impact of climatic conditions on production and quality at the armory was significant, as the lowest values of silymarin content and seed production were recorded in the year with drought conditions between March and May (Arampatzis et al., 2019).

Limiting factors are related to the presence of weeds. Pendimethalin and metribuzin are safe for weed control in armory, alone or in combination (Karkanis et al., 2011).

Morazzoni and Bombardelli (1995) stated that silybin, the main constituent of silymarin, accumulates better in subtropical climates, not in temperate ones, because higher temperatures seem to increase the accumulation of that compound. Results obtained in Poland and its neighbouring countries demonstrated that milk thistle accumulates more silymarin in warm years and when exposed to even rainfall distribution in May and June and a high phosphorus and nitrogen fertilization as well as that a delayed harvest date enhances the level of silymarin in fruit (Andrzejewska and Skinder (2006) cited by Andrzejewska and Sadowska (2008)).

Conclusions

Milk thistle is a plant with moderate requirements for water, but demanding for light and heat, which accumulates in its fruits a complex of phytochemical compounds that are very useful in various ailments, but especially for treating liver disorders. Among these compounds, silymarin is the best known. Due to its importance, numerous researchers have studied the uses of milk thistle, as well as different methods of increasing seed production and seed quality.

References

Abenavoli L., Milic N., 2017, Silymarin for Liver Disease. Liver Pathophysiology. Chapter 45:621-631.

AbouZid S.F., Chen S.N. and Pauli G.F., 2016, Silymarin content in *Silybum marianum* populations growing in Egypt. Industrial crops and products, 83:729-737.

Alemardan A., Salehi R., Karkanis A., 2013, Breeding objectives and selection criteria for milk thistle (*Silybum marianum* (L.) Gaertn) Improvement. Notulae Botanicae Horti Agrobotanici Cluj-Napoca 41(2):340-347.

Andrzejewska J. and Sadowska K., 2008, Effect of cultivation conditions on the variability and interrelation of yield and raw material quality in milk thistle (*Silybum marianum* (L.) Gaertn.). Acta Scientiarum Polonorum. Agricultura, 7(3):1-9.

Arampatzis D.A., Karkanis A.C., Tsiropoulus N.G., 2019, Impact of plant density and mepiquat chloride on growth, yield, and silymarin content of *Silybum marianum* grown under mediterranean semi-arid conditions. Agronomy 9(11):669.

Bahmani M., Shirzad H., Rafieian S., Rafieian-Kopaei M., 2015, *Silybum marianum*: Beyond Hepatoprotection. Journal of Evidence-Based Complementary & Alternative Medicine, 20(4):292-301.

Bhattacharya S., 2011, Phytotherapeutic properties of milk thistle seeds: An overview. Journal of Advanced Pharmacy Education&Research 1:69-79.

Buxbaum H., Kleifeld Y., Blumenfeld T., Herzlinger G., Chilft T., Gokkes M., 1999, Weed control in ornamentals and flowers. Phyparasitica, 27(2).

Cwalina-Ambroziak B., Wierzbowska J., Damszel M., Bowszys T., 2012, The effect of mineral fertilization on achenes yield and fungal communities isolated from the stems of milk thistle *Silybum marianum* (L.) Gaertner. Acta Sci Pol Hortorum Cultus; 11 (4):157-168.

Ferenci P., Dragosics B., Dittrich H., Frank H., Benda L., Lochs H., Meryn S., Base W. Schneider B., 1989, Randomised controlled trial of silymarin treatment in patients with cirrhosis of the liver. J.Hepatol. 9:105-113.

Druțu C., 2015. Tehnologia de cultivare la armurariu, planta medicinală care vă poate aduce profituri generoase. In https://www.stiriagricole.ro/tehnologia-de-cultivare-la-armurariu-planta-medicinala-care-va-poate-aduce-profituri-generoase-29709.html

Gabay R., Plitmann U., Danin A., 1994, Factors affecting the dominance of *Silybum marianum* L. (Asteraceae) in its specific habitats. Flora: 189:201-206.

Geller L.I., Gladkiks L.N., Griaznova M.V., 1993, Treatment of fatty hepatosis in diabetics. Probl. Endokrinol. 39:20-22.

Gresta F., Avola G., Guarnaccia P., 2006, Agronomic characterization of some spontaneous genotypes of milk thistle (*Silybum marianum* (L.) Gaertn.) in mediterranean environment. J. Herbs, Spices & Med. Plants 12:51-60.

Groves R.H., Kaye P.E., 1989, Germination and phenology of seven introduced thisthe species in Southern Australian Journal of Botany 37:351-359.

Hendawy S.F., Hussein M.S., Youssef A.A., El-Mergawi R.A., 2013, Response of *Silybum marianum* plant to irrigation intervals combined with fertilization. Nusantara Bioscience 5:22-29.

Houachri T., Bolonio D., Llamas A., Rodríguez-Fernández J., El Gazzah M., Mittelbach M., 2017, Fatty acid methyl and ethyl esters obtained from rare seeds from Tunisia: *Ammi visnaga*, *Citrullus colocynthis*, *Datura stramonium*, *Ecballium elaterium* and *Silybum marianum*. Energy Sources, Part A: Recovery, Utilization and Environmental Effects. Vol. 40(1):93-99.

Ismail E.G., Mohamed W.W., Khatta B.S., El Sherif F., 2013, Effect of manure and bio-fertilizer on growth, yield, silymarin content and protein expression profile on *Silybum marianum*. Int.J.Med.Arom.Plants 3(4):430-438.

Kapahi B.K., Balyan S.S., Srivastava T.N., Sarin Y.K., 1995, Cultivation of *Silybum marianum* Gaertn. A promising medicinal plant. Ancient Science of Life. XIV (4):240-244.

Karkanis A., Bilalis D., Eftimiadou A., 2011, Cultivation of milk thistle (*Silybum marianum* (L.) Gaertn), a medicinal weed. Indust. Crops and Products 34:825-830.

Keshavarz A., Chaichi R., Assareh M.R., Hashemi M.H., Liaghat M., 2014, Interactive effect of deficit irrigation and soil organic amendments on seed yield and flavonolignan production of milk thistle (*Silybum marianum* L. Gaertn.). Industrial Crops and Products, 58:166-172.

Lucini L., Kane D., Pellizzoni M., Ferrari A., Trevisi E., Ruzickova G., 2016, Phenolic profile and in vitro antioxidant power of different milk thistle

[*Silybum marianum* (L.) Gaertn.] Cultivars. Industrial Crops and Products, 83:11-16.

Luper S., 1998, A review of plants used in the treatment of liver disease: part 1. Altern Med Rev; 3:410-421.

Libster M., 2002, Delmar′s integrative herb guide for nurses. Thomson Learning. pp:669-677.

Martinelli T., Potenza E., Moschella A., Zaccheria F., Benedettelli S., Andrzejewska J., 2016, Phenotypic evaluation of a milk thistle germplasm collection: fruit morphology and chemical composition. Crop Science 56(6):3160-3172.

Montemurro P., Fracchiolla M. and Lonigro A., 2007, Effects of some environmental factors on seed germination and spreading potentials of *Silybum marianum* Gaertn. Ital J Agron. Riv Agron, 3:315-320.

Morazzoni P. and Bombardelli E., 1995, *Silybum marianum* (*Carduus marianus*). Fitoterapia; LXVI: 3-42.

Muntean L.S., 2003, Mic tratat de Fitotehnie, Vol. III, Tutunul, Hameiul, Plantele medicinale şi aromatice. Ed. Risoprint, Cluj-Napoca.

Muntean L.S., Tămaş M., Muntean S., Muntean L., Duda M.M., Vârban D.I. and Florian S., 2016, Tratat de plante medicinale cultivate şi spontane, Ed. Risoprint Cluj-Napoca, 928 p, ISBN 978-973-751-463-9, pp. 598-602.

Omidbaigi R., Nobakht A., 2001, Nitrogen fertilizer affecting growth, seed yield and active substances of milk thistle (*Silybum marianum*). Pakistan J.Biol.Sci. 4(11):1345-1349.

Pârvu C., 1991, Universul plantelor. Mica Enciclopedie. Ed. Enciclopedică.

Porwal O., Sheet M., Anwer Bayrakdar E.T., Uthirapathy S., 2019, *Silybum marianum* (milk thistle): review on its chemistry, morphology, ethno medical uses, phytochemistry and pharmacological activities. Journal of Drug Delivery and Therapeutics; 9(5):199-206.

Piazza G.J. and Foglia T.A., 2001, Rapeseed oil for oleochemical usage. European journal of lipid science and technology, 103(7):450-454.

Rahimi A. and Kamali M., 2012, Different planting date and fertilizing system effects on the seed yield, essential oil and nutrition uptake of milk yhistle (*Silybum marianum* (L.) Gaertn.). Advances in Environmental Biology 6(5):1789-1796.

Růžičková G., Fojtová J. and Součková M., 2011, The yield and quality of milk thistle [Silybum marianum (L). Gaertn.] seed oil from the perspective of environment and genotype-a pilot study. Acta fytotechnica et zootechnica, 14(1):9-12.

Sersen F., Vencecel T., Annus J., 2006, Silymarin and its components scavenge phenyl glyoxylicketyl radicals. Fitoterapia 77:525-529.

Smith T., Lynch M.E., Johnson J., Kawa K., Bauman H., Blumenthal M., 2015, Herbal dietary supplement sales in US increase 6.8% in 2014. HerbalGram. 107:52–59.

Stanceva I., Youssef A.G., Geneva M., Iliev L., Georgiev G., 2008, Regulation of Milk Thistle (*Silybum marianum*) Growth, Seed Yield and Silymarin Content with Fertilization and Thidiazuron Application. The European Journal of Plant Science and Biotechnology 2(1):94-98.

Timmerman B.N., Steelink C., Loeweus F.A., 1993, Phytochemical adaptation to stress. Vol.18, Plenum Press New York p. 338.

Tudora C., 2011, Tehnologii de cultivare a plantelor medicinale şi aromatice în zona Călăraşi-Silistra. In https://www.incdsb.ro/p/medplanet/doc/Curs%20 tehnologii%20de%20cultivare%20RO.pdf

Wallace S., Vaughn K., Stewart B.W., Viswanathan T., Clausen E., Nagarajan S., Carrier D.J., 2008, Milk thistle extracts inhibit the oxidation of low-density lipoprotein (LDL) and subsequent scavenger receptor-dependent monocyte adhesion. J Agric Food Chem. 56:3966-3972.

Wierzbowska J., Bowszys T., Sternik P., 2012, Effect of a nitrogen fertilization rate on the yield and yield structure of milk thistle (*Silybum marianum* (L.) Gaertn.). Ecological Chemistry and Engineering. 19(3):295-300.

Wierzbowska J., 2013, Effect of fertilization on the content of macronutrients in fruits of milk thistle (*Silybum marianum* L. Gaertn.). Journal of Elementology 18(4):723-732.

Zheljazkov V.D., Zhalnov I. and Nedkov N.K., 2006, Herbicides for weed control in blessed thistle (*Silybum marianum*). WeedTech.20:1030–1034.

Zohary M., 1962, Plant life of Palestine (Israel and Jordan). New York, USA Ronald Press Co., p. 262.

***https://plantatlas.brc.ac.uk/plant/silybum-marianum, accessed on 26 November 2022

*** www.faostat.fao.org, accessed on 26 September 2022

*** https://en.wikipedia.org/wiki/Silybum_marianum, accessed on 11 November 2022

***https://cstsp.md/uploads/files/Catalogul%20Soiurilor%20de%20Plante%2020 22.pdf - accessed on 28 November 2022

***https://istis.ro/image/data/download/catalog-oficial/CATALOG%202022%20-%20Monitor%2021%20iulie.pdf - accessed on 28 November 2022