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REVIEW ARTICLE

Interacting Environmental Factors Affect Targeted Milk Thistle Metabolomic Profile and other Growth Components: A Review

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ABSTRACT

Background: Milk thistle (*Silybum marianum* L. Gaertn.) is a medicinally important herb of the family Asteraceae. Its achenes contain the active compound silymarin, which has gained significant attention in the pharmaceutical industry for its hepatoprotective properties, including protection against hepatotoxic agents and stimulation of liver regeneration. However, biosynthesis and accumulation of active ingredients are strongly influenced by environmental variability.
Objective: To provide an inclusive overview of the physiological and phenotypic variations in milk thistle under different abiotic and biotic stresses, with a particular focus on silymarin synthesis and accumulation.
Methodology: A literature-based review was conducted, compiling information from available sources regarding germination, growth behavior, and secondary metabolite production of milk thistle under variable environmental conditions.
Results: Milk thistle not only serves as a medicinally valuable plant but also behaves as a noxious weed. Its germination, growth, and metabolite accumulation, especially silymarin, are highly affected by environmental factors. Despite available research, the full potential of this plant under diverse environmental conditions remains underexplored.
Conclusion: Milk thistle can adapt and grow under diverse conditions. However, stresses such as salinity, temperature, and rainfall adversely affect its growth and development, particularly silymarin production. Understanding the physiological responses and secondary metabolite production of milk thistle under different environmental stresses is crucial for optimizing its medicinal use and managing its weed potential in agriculture.

INTRODUCTION

Cells, organs, tissues, and metabolic functions at different developmental stages respond differently to environmental conditions. Environmental stresses pose serious challenges to agriculture by increasing consumption demands, limiting land availability, and reducing plant-derived medicinal product yields. Abiotic stresses exert considerable influence on the synthesis of secondary metabolites (Jaleel *et al*. 2007, Zahra *et al*. 2022). Milk thistle (*Silybum marianum* L. Gaertn.) is distributed across several countries but is specifically indigenous to Mediterranean regions. It grows at diverse altitudes, ranging from 700 to 1100 m, and thrives in sub-mountainous to coastal areas (Morazzoni and Bombardelli 1995). It can tolerate a wide range of pH but grows best at 5.5 to 7.6 (Andrzejewska and Sadowska 2008). As a dietary supplement, it is ranked among the top ten and is widely used for liver- and bile-related diseases (Kurkin 2003). Its achenes contain 20–35% fatty oil (Ramasamy and Agarwal 2008). Its oil is rich in vitamins (El-Mallah *et al*. 2003). Medicinally, milk thistle is used to treat gallbladder and various liver diseases (Abenavoli *et al*. 2010). It also hinders cholesterol biosynthesis, reduces certain cancer risks, and inhibits leukotriene production. Smith *et al.* (2008) reported that silymarin sales reached approximately 16.6 million USD in 2018 due to the presence of bioactive compounds. Its medicinal importance lies in the active compound silymarin, an isomeric mixture of flavonolignans including silychristin, silydianin, isosilybin, and silybin (Afshar *et al*. 2014). Silybin, a major component of silymarin, is in high demand due to its anti-carcinogenic properties. Silymarin stabilizes cell

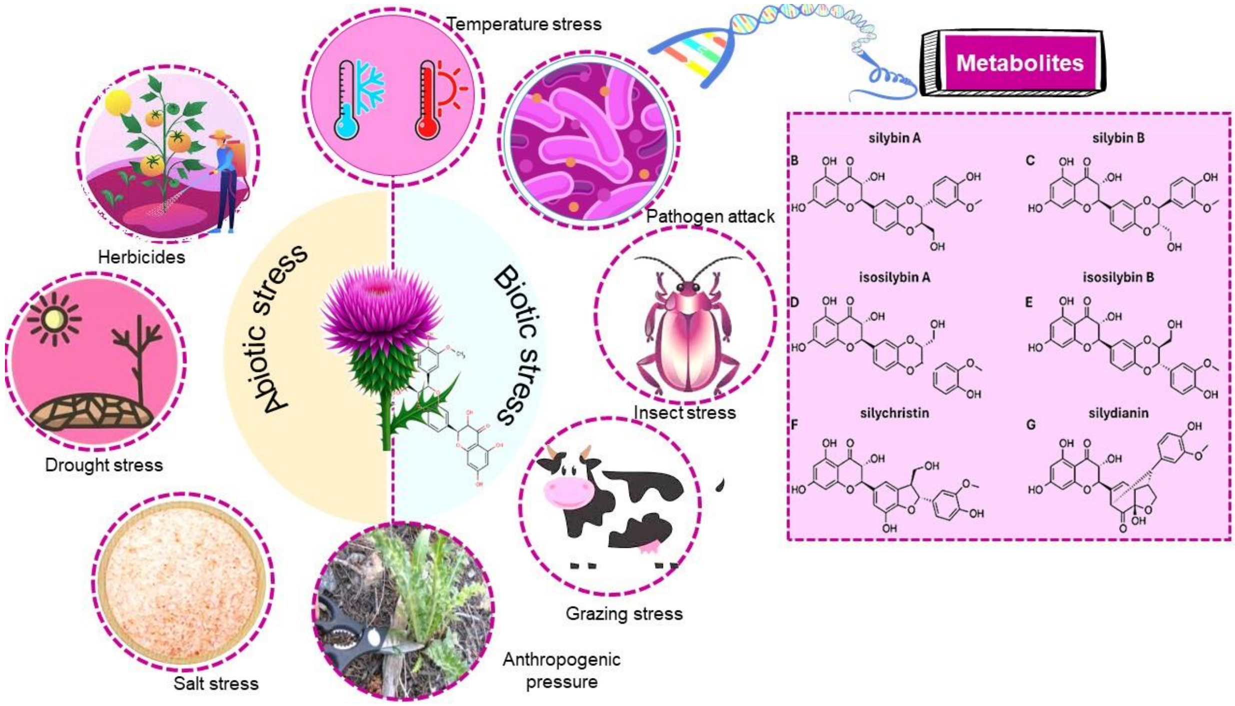

Fig. 1: Illustration of abiotic and biotic stresses affecting milk thistle

membranes, prevents hepatotoxic damage and stimulates liver regeneration (Fraschini *et al*. 2002).

The production of secondary metabolites is genetically and environmentally regulated, varying across plant families. Such metabolites enable plants to cope with severe environmental stresses and are used as therapeutic agents. Metabolic pathways and active substances are also severely affected by environmental stresses (Bohnert *et al*. 1995). Their biosynthesis and accumulation depend strongly on soil properties (Selmar and Kleinwachter 2013). Silymarin content in achenes is influenced by both genotypic variation and environmental conditions (Ghavami and Ramin 2008). Interestingly, silybin content was reported to be higher in cultivated ecotypes, whereas isosilybin, silydianin, and silychristin levels were higher in native ecotypes (Radjabian *et al.* 2008). Milk thistle can adapt and grow under diverse conditions. However, stresses such as salinity, temperature, and rainfall adversely affect its growth and development, particularly silymarin production (Fig. 1). However, no comprehensive review is present on the effect of biotic and abiotic stresses on milk thistle production and metabolites synthesis. Being one of the most important medicinal plants for treating liver diseases in humans, understanding its ecophysiological behavior is crucial for promoting large-scale cultivation. This review applies a nonlinear regression model to describe milk thistle's responses under different stresses and to highlight the challenges faced in its cultivation and utilization. Such insights can guide future research and support sustainable production.

ABIOTIC STRESSES

Milk thistle under salinity stress

Germination of plants faces a life-threatening challenge in salt marshes and saline desert areas, leading to the mortality of germinating plants. However, different plant species have their own salinity tolerance mechanisms (Brady and Weil 1996). In general, satisfactory achene germination of milk thistle was recorded up to 6 dS/m salinity stress. A 50% reduction in achene germination and seedling emergence was reported at a salinity level of 9 dS/m. Significant reductions in the number of leaves per plant, main capitulum per plant, achene weight per capitulum, achene weight per plant, and 1000 achene weights were observed at 9 dS/m salinity stress. However, at the 15 dS/m salinity level, plants still produced achenes, but the yield was one-third compared to the control. At low salinity (< 9 dS/m), milk thistle shows limited growth and no effect on grain yield compared to control plants, which is why it is categorized as a facultative halophyte (Ghavami and Ramin 2007). Sedghi *et al.* (2010) recorded a severe reduction of growth attributes of milk thistle seedlings under salinity, including plumule and radicle length, plumule fresh and dry weight, and germination percentage with increasing salinity. Maximum reduction was observed at 10 dS/m. Kashmir *et al.* (2016) documented that salinity levels up to 100 mM had a non-significant effect on germination and growth-related parameters of milk thistle, but concentrations higher than

Xiao-fang *et al.* (2000) also found that germination percentage decreased with increasing salinity. Similarly, Ghanbari *et al.* (2013) reported that shoot and root growth were negatively affected under salinity in milk thistle. Moreover, Solouki *et al.* (2015) also reported that increasing Na^+ concentration decreased germination time, germination percentage, seedling number, coefficient of germination time, radicle length, vigor index, seedling length, plumule fresh weight, and radicle fresh weight. Safikhan *et al.* (2018) reported that salt stress, especially salinity levels of 8 and 12 dS/m, decreased growth as well as other biochemical attributes, including chlorophyll content, carbohydrates, enzymatic activity, and proline concentration. Hydrogen peroxide (H_2O_2) concentration also increased, indicating stress severity. It was concluded that salt stress, especially under 8 and 12 dS/m, decreased growth characteristics and chlorophyll content, while proline, carbohydrates, enzymatic activity, and H_2O_2 concentration increased in milk thistle leaves (Fig. 2). Little information has been published regarding the correlation of active substances, yield components, and grain yield under salinity stress in milk thistle (Omidbaigi and Nobakht 2001). Maximum oil content was observed up to 6–9 dS/m salinity level; however, further increase in salinity levels gradually decreased oil content. The positive effect of salinity stress on achene silymarin and silybin content has also been reported (Ghavami and Ramin 2008). Similarly, Zahra *et al.* (2021a; 2021b; 2022) also reported that silymarin content was enhanced under salinity stress, while severely deteriorating all growth and yield parameters.

In crux, salinity stress adversely affects the growth and yield attributes. Moreover, salinity stress increased the production of silymarin and silybin, which are medicinally important phytochemicals present in the achene. However, further research is required to explore its metabolic shifts under a saline environment.

Milk thistle and drought stress

Worldwide, plant growth and development are severely affected by drought stress, especially in arid and semi-arid regions (Afshar *et al.* 2014). Deliri *et al.* (2010) worked on different milk thistle ecotypes and observed that ecotypic differences are highly significant in relation to drought stress. They emphasized that decreases in chlorophyll content, dry weight, root volume, and root tolerance index, along with an increase in electrolyte leakage, are related to drought stress severity. Moreover, Afshar *et al.* (2015) also noted that silymarin content increases in drought-affected milk thistle achenes. Furthermore, they elaborated that the amount of silybin increased under water stress, which is a more biologically active compound compared to others. Zahir *et al.* (2014) found enhanced accumulation of total flavonoids and phenolic content in drought-affected milk thistle. Malekzade *et al.* (2011) proved that milk thistle oil increased under drought stress. A high content of unsaturated fatty acids accumulated under severe drought stress. Ghassemi-Golezani *et al.* (2017) reported that under water stress, harvest index, 1000 achene weight, achene yield per plant, number of achenes per plant, and plant biomass decreased. Furthermore, oil percentage and yield also decreased; however, flavonoid content increased in water-stressed milk thistle.

Essential oil levels are significantly reduced under acute water stress. Afshar *et al.* (2016) evaluated that relative water content, stem diameter, leaf dry weight, and leaf area remained unaffected under moderate drought and were only affected under severe drought stress. They observed a decrease of about 19 and 44% in photosynthesis under moderate and severe drought stress, respectively. Moreover, Zahir *et al.* (2014) elaborated that water deficiency inhibited shoot and root growth; however, total phenolic content, total protein, antioxidant enzymes, and flavonoids increased under drought stress (Table 1). The potential use of drought stress is to enhance the production of active compounds, especially phenolic compounds (Bettaieb *et al.* 2009). It has been observed that under drought stress, the total flavonoid and phenolic content increase in milk thistle (Zahir *et al.* 2014). A significant increase in silymarin accumulation and synthesis was observed in milk thistle achenes under drought stress. So, severe and moderate drought stress enhanced silymarin by 4 and 17% respectively, compared to the control. Under drought conditions, silymarin, silychristin, isosilybin, and silybin also increased, but decreased silydianin content (Afshar *et al.* 2015). A decrease in grain yield of milk thistle was also reported under drought, so the enhanced concentration of silymarin is not economically beneficial according to Afshar *et al.* (2014). In conclusion, drought stress causes a severe reduction of all the growth and yield-related traits but enhances its medicinally important secondary metabolite production. The production of these metabolites is stress stress-relieving strategy, but their metabolic profile characterization under mild stress may play a plausible role in uplifting its economic benefits.

Milk thistle under temperature stress

Temperature is an important abiotic factor that influences plant growth and development. Rahman *et al.* (2016) documented that temperature changes have regulatory effects on plant height, number of flowers per plant, number of achenes per plant, and crop yield per hectare. Milk thistle achene germination, germination percentage, and the number of seedlings at 15 °C were higher compared to 25 or 35°C. Germination percentage was about 95 and 70% under 15 and 35°C, respectively (Ghavami and Ramin 2007). Kashmir *et al.* (2016) reported that 25°C (optimum temperature) resulted in higher growth and germination rates; however, lower (15°C) and higher temperatures (40°C) resulted in poor germination and growth. Pourreza and Bahrani (2012) reported that temperatures ranging from

Table 1: Changes in silymarin content under different stresses

Stress	Change in silymarin contents	References
Salinity stress	Silymarin ↑; Silybin ↑	Ghavami and Ramin (2008)
Drought stress	Silymarin ↑	Afshar *et al.* (2014); Afshar *et al.* (2015);
	Silymarin + silybin A & B ↑	Shawky (2015)
	Silymarin ↓	Afshar (2015)
	Oil ↑	Malekzade *et al.* (2011)
	Silymarin ↑	Zahir *et al.* (2014)
	Silymarin ↓	Afshar (2014)
Density	Silymarin ↑	Azizi *et al.* (2018); Katar *et al.* (2013)
Heavy metal	Silymarin is not affected	Rio-Celestino *et al.* (2006)
Herbicides	Silymarin ↑	Zheljazkov (2006)
Metribuzin bentazon	Silymarin ↓	Zheljazkov (2006)
Higher population	Not affected —	Omer *et al.* (1993)

Fig. 2: Milk thistle necrosis under salinity stress

21–27°C were effective in enhancing germination percentage. Heidari *et al.* (2014) used three varieties of milk thistle to confirm cardinal temperatures related to germination response. They concluded that varietal and temperature differences are of prime importance, especially regarding germination rate, reciprocal time to 50% germination, germination uniformity, germination percentage, and time to 5, 10, 50, 90, and 95% germination. They suggested that the optimum temperature for milk thistle growth is 28–29.5°C.

Milk thistle under heavy metal stress

Milk thistle often faces heavy metal stress due to its cosmopolitan nature. Khatamipour *et al.* (2011) reported that cadmium toxicity affected germination rate, germination percentage, seedling growth, fresh and dry weight of shoot and root, and shoot and root length of milk thistle. They also concluded that all concentrations of cadmium (Cd) slightly increased the shoot/root ratio and proline content. Moreover, results indicated that roots were more affected by Cd than shoots. Several researchers reported that milk thistle can grow well in contaminated soils with heavy metals such as zinc (Zn), manganese (Mn), copper (Cu), lead (Pb), chromium (Cr), and Cd (Zheljazkov and Nikolov 1996), and even tolerates the radioactive element cesium (Cs). Zheljazkov and Nikolov (1996) reported that Zn accumulated mainly in leaves and stems, while Mn, Cu, Pb, and Cd accumulated in leaves and roots. Achene yield decreased by 16% under heavy metal stress compared to the control. It was noted that the species can accumulate zinc and lead and can also relocate them to the harvestable parts. For this reason, Del Rio-Celestino *et al.* (2006) suggested that milk thistle is not a hyperaccumulator. However, silymarin content remained unaffected under heavy metal stress (Zheljazkov and Nikolov 1996). According to Ikram *et al*. (2025), arsenic (As) stress increased silymarin production up to 80%, and they suggested that increasing its production plays a pivotal role in neutralizing stress and initiating tolerance mechanisms.

BIOTIC STRESSES

Effect of insect attack on milk thistle

Milk thistle is susceptible to insect attack. For instance, Goeden (1971) noticed that an assemblage of phytophagous insects fed or reproduced on milk thistle plants, but apparently no deleterious effect was observed on the root, stem, or reproductive parts of milk thistle. *Rhinocyllus conicus* (weevil) attacks thistle genera *Onopordum*, *Carduus*, *Cirsium*, and *Silybum* (Fig. 3) (Goeden and Ricker 1974). *R. conicus* larvae were also found in the achene tissues and achene heads of milk thistle (Coombs *et al*. 1996). Clarke and Walter (1993) observed that *Nezara viridula* infects milk thistle in Queensland, Australia. Abdel-Moniem (2002) reported the presence of the achene head weevil (*Larinus latus* Herbst) on milk thistle. They noted that weevil achene larvae have an injurious effect on the flower head. A single larva can destroy all the achenes of a flower head ranging from 2 to 3 cm in diameter. In Greece and Iran, *Aphis fabae cirsiiacanthoidis* and *Dysaphis lappae cynarae* are well-known aphids (Fig. 3) that attack milk thistle plants (Kavallieratos *et al.* 2007; Rezwani 2008). Khan *et al.* (2009) observed that caterpillars of *Spodoptera* sp. damage leaves at the end of flowering. Snails are pests recorded frequently in wet weather conditions. Abdel-Moniem (2002) reported a reduction in achene heads by *L. latus*. Dodd (1989) pointed out that weevils have restricted oviposition and low-density larvae per capitulum, with little effect on prolonged flowering of milk thistle. Scientists in Israel focused on dense plant occurrence near ant nests and achene dispersal by ants. Ants move the achene into their nest and remove the oily body (elaiosome) to feed their

Fig. 3: *Rhinocyllus conicus* attack on milk thistle

larvae, which increases milk thistle vigor and germination (Gabay *et al.* 1994).

Pest and disease attack

Pest and disease attacks on plants not only affect growth but also yield. Like other plants, milk thistle is also infected by various pests and microbes. *Septoria silybi* is a fungus that interferes with photosynthesis and causes leaf lesions (Moscow and Lindow 1989). Roche (1991) observed that *S. silybi* infects milk thistle plants during daylight when there is a high humidity inoculation period, but rare infestation was observed when light was excluded. The reason behind this infestation is related to the requirement for open stomata for pathogen penetration in milk thistle leaves. Berner *et al.* (2002) observed that the rust fungus *Puccinia punctiformis* is a pathogen of Canada thistle but often affects milk thistle. El-Elimat *et al.* (2014) isolated *Aspergillus iizukae* from the leaves of milk thistle. Souissi *et al.* (2005) suggested that *Microbotryum silybum* (a smut fungus) is a naturally occurring pathogen of *Silybum marianum* (Tamouridou *et al.* 2018). Moscow and Lindow (1989) observed *S. silybi* infection in milk thistle plants over several years in central California. Saccardo (1884) and Oudemans (1923) reported that *S. silybi* is the only pathogen on the sole host of milk thistle. Moscow and Lindow (1989) conducted a detailed experiment on *S. silybi*-infected milk thistle and reported that it can survive under dry periods when rain and dew are inadequate. A very low inoculum of *S. silybi* spores is enough to cause considerable infection, leading the leaves to become necrotic. Under high inoculum, severe disease was observed with numerous necrotic leaves that reduced plant growth and eventually killed the plant (Jamali 2015). *Puccinia cruchetiana*, *P. tyrimni*, *P. mariana* and *P. laschii* also cause infestation in milk thistle (Brandenburger 1985). Kováčiková and Kubínek (1986) noted that milk thistle is severely infected by the *Fusarium* genus. Cwalina-Ambroziak *et al.* (2012) reported approximately six species of this genus that infect milk thistle. Šafránková *et al.* (2015) observed mildew, *Golovinomyces orontii* on milk thistle during the vegetation period. Besides, gray mold (*Botrytis cinerea*) was observed during the rainy season. At the achene ripening stage, vast infestation was observed on stems, leaves, and anthodia. Additionally, they observed the presence of *Fusarium* and *Rhizoctonia* sp. on milk thistle roots and *Rhizoglyphus* sp. infection on roots and root collars. Milk thistle is also a host for cucumber mosaic virus (Souissi *et al.* 2005) and tomato spotted virus (Chatzivasiliou *et al.* 2001). Furthermore, Chatzivasiliou *et al.* (2001) observed that it is also a host for TSWV (tomato spotted wilt virus).

Weed attack and milk thistle productivity

One of the most important limiting factors in the production of milk thistle is the lack of weed control (Topalov *et al.* 1983). Zheljazkov *et al.* (2006) noted 16 species, of which the most abundant were green foxtail (*Setaria viridis* L. Beauv.), bermudagrass (*Cynodon dactylon* L. Pers.), and redroot pigweed (*Amaranthus retroflexus* L.). The most observed perennials were monocotyledonous johnsongrass (*Sorghum halepense* L. Pers.), Canada thistle (*Cirsium arvense* L.), motherwort (*Leonurus cardiaca* L.), and bindweed (*Convolvulus arvensis* L.). Other weed species included large crabgrass (*Digitaria sanguinalis* L.), prostrate pigweed (*Amaranthus blitoides* S. Wats.), velvetleaf (*Abutilon theophrasti* Medik.), common cocklebur (*Xanthium strumarium* L.), black nightshade (*Solanum nigrum* L.), prostrate knotweed (*Polygonum aviculare* L.), wild buckwheat (*P. convolvulus*), jimsonweed (*Datura stramonium* L.), and common lambsquarters (*Chenopodium album* L.). They also documented that the highest infestation was found in untreated milk thistle plants.

Animal attack

The achene bank for milk thistle is very limited (Sofer-Arad *et al.* 2007), and continuous grazing might control this species within a few years (Fig. 4). The density of milk thistle is severely affected by cattle grazing, including rotational and continuous grazing (De Bruijn and Brok 2006). However, Sofer-Arad *et al.* (2007) observed that cattle grazing may be associated with higher thistle frequency in the mid-eastern rangelands. Spines in milk thistle deter cattle, thus hampering grazing (Danin and Yom-Tov 1990). Grazing milk thistle is toxic for cattle due to lethal and high content of nitrates (Clark County Noxious Weed Program; CCNWP 2015). Campbell *et al.* (1979) reported that goats can limit milk thistle biomass and reduce achene production. Goats will graze on milk thistle, but less than 1% of achenes pass through their digestive tract (Sindel

Fig. 4: Animal attack on milk thistle

1991). Vinograd *et al.* (2011) reported that in Israel, milk thistle is a dominant weed and cannot be grazed by sheep and goats.

Milk thistle and population density

Population density and row spacing between plants have a significant effect on growth, yield, and active compounds of milk thistle. Austin *et al.* (1988) maintained eight plants per pot (18 cm diameter pot) and found the highest shoot yield after 6 weeks of plantation, while a decrease in shoot yield was observed with increased density of plants per pot. Gabucci *et al.* (2002) noted that higher population density decreased achene yield, number of blooms per plant, and bloom diameter. Belitz and Sams (2007) observed that achene yield decreased when population density increased, showing a negative correlation between yield, mature achene counts, bloom diameter, number of blooms per plant, and population density. Contrarily, Duran Katar *et al.* (2013) reported that higher population density increased achene yield and silymarin content in milk thistle. They found a higher yield (83.13 kg ha^{-1}) and silymarin (1.413 kg ha^{-1}) at a sowing density of 40,000 plants ha^{-1}. Omidbaigi *et al.* (2003) concluded that 50 × 30 cm is the most suitable density for milk thistle. Recently, Azizi *et al.* (2018) observed the tallest plants, the highest grain, and biological yield at 8 plants m^{-2} density. Moreover, they noted that population density had no impact on silymarin concentration. However, Omer *et al.* (1993) noted that narrow row spacing of approximately 25 cm increased achene yield but decreased flavonolignan and oil content compared with 50 cm spacing in milk thistle. They also found that row spacing greater than 25 cm significantly increased silymarin, isosilybin, silychristin, and silybin concentrations.

Anthropogenic activities

Milk thistle is a noxious weed that is harmful to economic and environmental resources; therefore, plants are targeted for eradication. It has pappi-bearing achenes that are easily pollinated even before harvest, thus emerging as a weed for the next crops. In North America, it is classified as a noxious weed in Washington (category A), Oregon (category B), and Texas (category S2) (Plant Protection and Quarantine 2002), but no case has been reported from Canada (USDA-ARS 2005). A limiting factor for milk thistle production is weed control. Milk thistle is very sensitive to herbicides used for other crops (Topalov *et al.* 1983). Parsons (1973) noted that it is very easy to eradicate milk thistle plants with several herbicides; however, large flowering and rosette plants are difficult to kill. Shimi *et al.* (2006) observed that clopyralid (0.24 kg ha^{-1}) can control 94% of milk thistle growth. In cereals, 2,4-D ester and MCPA, 2,4-D amine can be used to control milk thistle (Department of Primary Industries, Water and Environment, 2008). Zand *et al.* (2007) noted that bromoxynil plus MCPA at 560 g ha^{-1}, metsulfuron plus sulfosulfuron at 36 g ha^{-1}, and chlorsulfuron at 10.5 g ha^{-1} suppressed milk thistle achene production. So, these herbicides also affect the milk thistle production.

CONCLUSION

Milk thistle (*Silybum marianum* L. Gaertn.) is a valuable medicinal plant recognized for its hepatoprotective, antioxidant, and anti-inflammatory properties, primarily attributed to its bioactive compound silymarin. Despite its therapeutic potential, milk thistle faces several abiotic and biotic stresses, including drought, salinity, heavy metals, insect pests, diseases, weeds, and grazing pressure, which significantly affect its growth, yield, and active constituents. Research findings indicate that appropriate agronomic practices, such as optimized population density, nutrient management, and protective measures against pests and weeds, can improve its productivity and phytochemical composition. Furthermore, its classification as both a medicinal resource and a noxious weed highlights the dual challenges in its management. Overall, milk thistle represents a promising plant species with significant pharmaceutical and ecological importance, but sustainable cultivation strategies are essential to maximize its benefits while minimizing its invasive potential.

DATA AVAILABILITY

Not applicable to this paper

ETHICS APPROVAL

Not applicable to this paper.

FUNDING SOURCE

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