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REVIEW PAPER

Silybum marianum – properties and application in medicine – a review

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ABSTRACT

Introduction and aim. The subject of this article is milk thistle – a plant belonging to the Asteraceae family. Due to its properties, it has a beneficial effect on the functioning of important organs and systems of the human body. The aim of this paper was to review information on milk thistle, its use in medicine and the description of some of the chemical compounds due to which it owes its healing properties.

Material and methods. The article is a review of the publicly available literature on milk thistle, the chemical composition of its compounds and its use in medicine.

Analysis of the literature. Current information about *Silybum marianum* is presented.

Conclusion. Milk thistle is a valuable medicinal plant due to the presence of numerous antioxidant and anti-inflammatory compounds. The benefits of supplementation with ingredients derived from milk thistle, their negligible interaction with other drugs and the lack of significant side effects, known so far, indicate that the plant described in the article can be a good medicine and a preventive measure against diseases affecting our society.

Keywords. milk thistle, silybin, silymarin

Introduction

The subject of this article is milk thistle - a plant belonging to the Asteraceae family. Due to its properties, it has a beneficial effect on the functioning of important organs and systems of the human body.[1-2] So far, the focus has been on its detoxifying effect and supporting liver regeneration, but the latest research shows that the compounds obtained from milk thistle show a broader health-promoting effect.[3-4] Due to the high potential of milk thistle as a raw material for medical use, the article will be a kind of review in which the habitat of this plant and its habit will be presented, as well as its use in medicine, along with a description of some chemical compounds thanks to which it owes its healing properties.[5-10]

Aim

A general overview of information on milk thistle, with particular emphasis on its use in medicine and the description of some of the chemical compounds due to which it owes its healing properties.

Material and methods

The review is based on the available literature on milk thistle, the chemical composition of its compounds and its use in medicine. The time of publishing the articles ranges from 1996 to 2022, with the oldest article describing the general appearance of the plant. In contrast, information on the properties of chemicals and their clinical effects is based on articles that describe

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research at the cellular level, animal studies, and clinical trials.

Analysis of the literature

Milk thistle (*Silybum marianum*) is a herbaceous, annual (under favourable conditions - biennial) plant belonging to the Asteraceae family and comes from the regions of the Mediterranean Sea, where it is most common today. However, it can be found all over the world, as it was introduced by man to various countries. In Poland, it occurs mainly as a plant cultivated to obtain valuable medicinal substances, sometimes it is treated as an ornamental plant, less often it occurs in a wild-growing form. Milk thistle is one of the plants that do not require special growing conditions, but its cultivation is favoured by a humid and warm climate and fertile soil. Under such conditions, *S. marianum* can reach a height of up to two metres, but the average height it grows is about 1.5 metres.[1-2,5-6] The plant looks like a thistle. It has a strong single or branching stem. Its leaves are broadly elliptical or oblong-ovate, sinus-lobed, dark green in colour, shiny and speckled with white spots. Older leaves end with yellow spikes. During flowering, which lasts from late June to mid-August, *S. marianum* has pink-purple flowers gathered in basket-shaped inflorescences about five centimetres in size. Additionally, as a honey plant it attracts insects, especially bees and butterflies.[2,5-6] The fruit of milk thistle is achenes – a non-bursting, dry fruit with a leathery pericarp with a single seed in it.[1] The fruits obtained during the autumn harvest (September to October) are a source of valuable substances used in medicine, such as flavonolignans.[1,2] The largest amount (even 98%) is accumulated in the pericarp and the husk of the achenes.[1]

Substances contained in milk thistle

Milk thistle is used to obtain silymarin extract (fig. 1.), i.e. a complex of flavonolignans. It consists of silybin (fig. 2.) in the form of two diastereoisomers (silybin A and B), isosilybin (fig. 3.) (also in the form of two diastereoisomers of isosilybin A and B), silychristin (fig. 4.), silydianin (fig. 5.) and the precursor of the above flavonolignans – taxifolin (fig. 6.).[2,7,11-16] As the predominant part of the silymarin complex, silybin is the compound responsible for its biological activity.

Due to the high proportion of silybin (figure 2) in silymarin, it is mistakenly identified with the entire complex of this compound. Like other flavonolignans, silybin is an antioxidant. Its molecular formula is $C_{25}H_{22}O_{10}$ and its molecular weight is 482.441 u. It consists of two units – one based on taxifolin, the other – a phenylpropanoid unit, which are linked together by an orexan ring. It exists as two diastereoisomers (silybin A, silybin B) and is biotransformed in the liver. It is poorly soluble in water and therefore has low bioavailability.[3-4] Most of the silybin is excreted in the bile in conjugated form with sulphates and glucuronides, some is excreted unchanged in the urine and the rest is eliminated in the faeces.[17-18] This compound exhibits antioxidant, anti-inflammatory (related to antioxidant properties), anti-fibrotic (by reducing platelet-induced DNA synthesis and cell proliferation) and modulating (in some liver metabolic pathways activity).[3] In addition, its interaction with some cytochromes and interference with the regulation of the cell cycle was discovered, which is a factor in preventing cancer. Due to the above properties, silybin shows an action similar to silymarin, however, studies indicate significant differences in the interactions of these compounds with metabolizing enzymes. Nevertheless, silybin is also used as a completely separate component of silymarin and research is conducted to increase its bioavailability and absorption by the human body.[18]

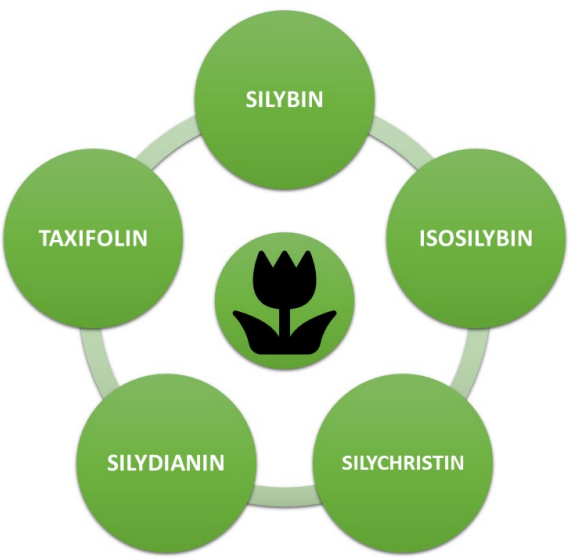

Fig. 1. Substances contained in Milk thistle

The composition of silymarin causes its low bioavailability when used orally due to poor water solubility, low absorption efficiency in the intestines, as well as the metabolism of the complex in the liver, which reduces the availability of this compound for the body's cells. To increase the efficiency of delivering silymarin to tissues and organs, it is administered in the form of a complex with the highly water-soluble antioxidant phosphatidylcholine and more soluble silymarin derivatives have been produced and administered to patients. Other substances increasing the bioavailability of this compound are the flavonoid found mainly in citrus fruits – tangeretin and piperine contained in black pepper. The increase in silymarin bioavailability allowed for more effective research on the health-promoting effect of this compound and its interaction with other medicinal substances.[3-4] Studies to date show that this compound does not interfere with the effects of medications used by patients and may alleviate

their side effects.[6,19] However, drug-drug interactions between silymarin and drugs have not been ruled out, and further detailed research is needed.

In therapeutic doses, the intake of silymarin does not show any toxic properties. It should also be mentioned that so far no serious side effects from the use of silymarin have been demonstrated. Cases associated with gastrointestinal disturbances such as diarrhoea and gastroenteritis have rarely occurred. Headaches or dermatological symptoms such as hives, itching or allergic dermatitis have also been reported.[3,20-21] Additionally, there were no documented contraindications to the use of silymarin preparations.[20]

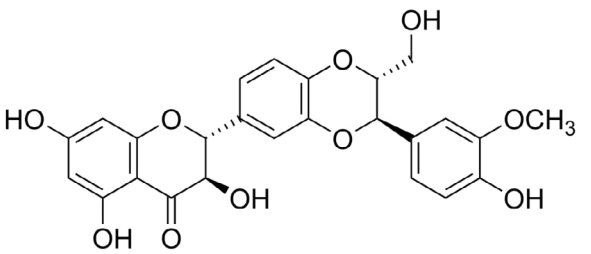

Fig. 2. Structural formula of silybin

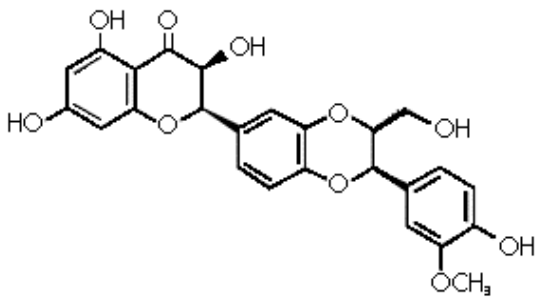

Fig. 3. Structural formula of isosilybin

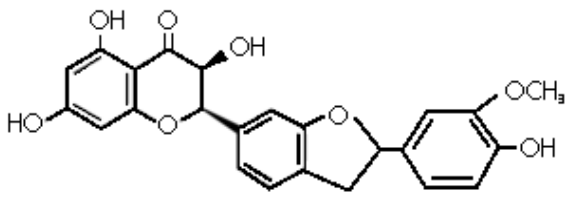

Fig. 4. Structural formula of silychristin

At this point, it is worth mentioning that milk thistle may be affected by some microfungi (eg. *Fusarium* or *Alternaria genera*) and their mycotoxins, contributing to the reduction of the beneficial effects of silymarin or even their complete elimination. The most important in this aspect are: alternariol methyl ether (AME), alternariol (AOH), beauvericin (BEA), deoxynivalenol (DON), enniatin A (ENNA), enniatin A_1 ($ENNA_1$), enniatin B (ENNB), enniatin B1 (ENNB1), HT-2 toxin (HT-2), T-2 toxin (T-2), tentoxin (TEN) and zearalenone (UAE). Their presence in supplements containing compounds isolated from milk thistle or in the plant itself may have a hepatotoxic, nephrotoxic, neurotoxic, teratogenic, immunosuppressive, genotoxic and even carcinogenic effect.[5]

At the same time, silymarin has been shown to be effective against the adverse effects of some mycotoxins. Many studies show its beneficial effect on weight gain and feed consumption by broilers treated with alphatoxin B1 (AFB1), as well as sensory and quality improvement of meat obtained from these animals.[5,22-23]

Research also indicates an improvement in the functioning of the immune system of Japanese quails after ingesting silymarin in their diet, as evidenced by a reduction in the relative weight of Fabrucius' capsule and spleen in these birds.[24] The effect of improving the immune response was also observed in broilers after feeding with milk thistle.[25]

Other compounds that, apart from silymarin are found in the seeds of milk thistle and its other parts include dietary fibre, proteins, sugars, polyunsaturated fatty acids (e.g. linoleic acid), monounsaturated fatty acids (e.g. oleic acid), phytosterols, alpha tocopherol, quercitin, histamine, tannins, minerals and vitamins.[2,7,18,26]

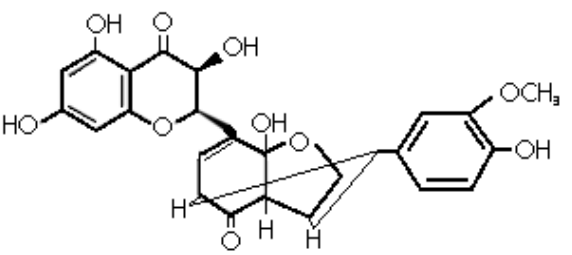

Fig. 5. Structural formula of silydianin

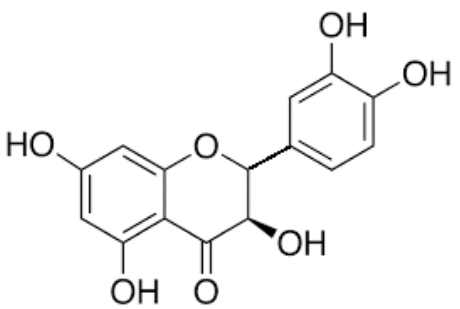

Fig. 6. Structural formula of taxifolin

The use of milk thistle in medicine

Thanks to the substances described above and their belonging to flavonoglycans, milk thistle shows valuable healing properties (Figure 7).

It interacts with some cytochromes and interferes with the regulation of the cell cycle. The effect of these substances is primarily hepatoprotective properties. They are based on the protection of liver cells against

harmful and toxic factors, such as alcohol or substances present in *Amanita phalloides* or *Amanita muscaria*.[6-7] Intravenous administration of silybin within 48 hours of poisoning at a dose of 2050 mg/kg per day, during 3-4 days completely inhibited liver damage. A study conducted on 250 people poisoned with *A. muscaria* indicated 46 deaths in the untreated group. However, among the 16 people who received silybin, there were no deaths.[9]

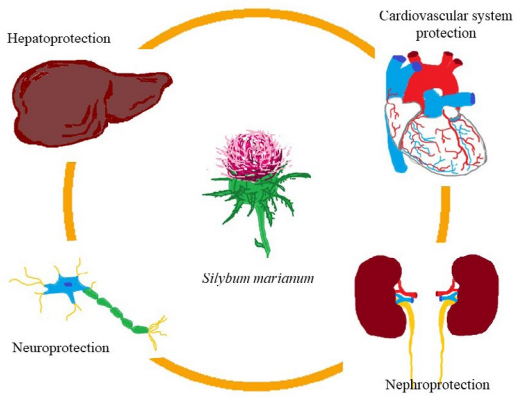

Fig. 7. Some healing properties of *Silybum marianum*

Another study involving 18 people poisoned with *A. muscaria* and treated with silybin resulted in only one death of a person who ingested the poison in order to commit suicide, with treatment not commenced until 60 hours after ingestion.[5] Protection of the liver against these factors mainly consists in improving the integrity of the hepatocyte membranes, which makes it difficult for the toxic factors to penetrate the liver cells.[10]

Other protective properties include antioxidant, antiviral and anti-inflammatory effects. In addition, the plant supports the regeneration of the liver damaged by both physical and chemical factors resulting from the metabolic function of this organ, while preventing the processes of fibrosis.[6-7] Accordingly, the hepatoprotective properties of milk thistle are used to alleviate and treat acute and chronic liver diseases such as non-alcoholic fatty liver disease, alcoholic cirrhosis, and viral hepatitis.[4,7,17]

Fatty liver is often associated with obesity, type 2 diabetes, insulin resistance and dyslipidemia. Nevertheless, the action of milk thistle also helps prevent these diseases by improving lipid metabolism. As a result of the use of preparations with silymarin, the excretion of low-density lipoproteins is increased, and the synthesis of cholesterol is reduced. The results of clinical trials also showed that the daily use of silymarin at a dose of 420 mg in 15 people with hypercholesterolemia led to lower cholesterol levels in the gallbladder compared to the control group. This suggests that silymarin may be introduced as a blood cholesterol reducer in patients with hypercholesterolemia.[6,27] It is of great importance for the proper functioning of the circulatory system, protecting against the formation of atherosclerotic plaques.[6,17]

The antioxidant properties of silymarin have a protective effect not only on the liver cells but also on the cells of other internal organs, such as the kidneys. This is because silymarin is concentrated in the cells of the kidneys, supporting their regeneration by increasing the synthesis of proteins and nucleic acids. On the other hand, the presence of silybin and silychristin in silymarin is attributed to an increase in cell replication by 30%.[5] It has been shown to prevent and reduce kidney damage resulting from cytostatics and to protect against radiation damage.[6-7,28-29] Additionally, the conducted studies indicate a beneficial therapeutic effect of silymarin in the development of diabetic nephropathy.[6]

Another effect of the substances contained in milk thistle is neuroprotection. As a result of the use of silymarin, the nerve conduction of nerve fibres improves, which suggests its use in the treatment of Alzheimer's disease.[5-6]

The use of milk thistle preparations also supports the lactation processes in breastfeeding women, has a positive effect on the bile ducts, spleen and pancreas. A beneficial effect of *S. marianum* seed oil on the skin was also found.[5,7,30]

An important aspect of the action of silymarin is the anti-cancer effect.[31] To date, its preventive activity has been demonstrated in the presence of prostate, breast, bladder, lung and ovarian cancer by inducing apoptosis of abnormal cancer cells. The substances contained in milk thistle also inhibit metastases accompanying neoplasms, including metastases to the brain.[6-8] It has also been proved that silymarin can reduce the undesirable effects of anti-cancer drugs such as paclitaxel, cisplatin, methotexate, and fluorouracil. However, there are concerns that the strong antioxidant activity of milk thistle may interfere in determining the lymphocytotoxicity function of chemotherapy drugs through biochemical peroxidative pathways.[5]

Conclusion

Milk thistle is a valuable medicinal plant due to the presence of numerous antioxidant and anti-inflammatory compounds. Although the mechanisms of their metabolism and the subsequent effects of the metabolized products on the cells of the human body are not fully understood, it cannot be denied that they ultimately exhibit hepatoprotective, antioxidant, immunomodulating and even anti-tumor effects. It is worth continuing research on the use of silymarin in diseases of the liver and biliary tract and introducing it into clinical practice as an adjunct to traditional therapy. However, additional research should be focused on the long-term effects of milk thistle and the interactions of its compounds with other drugs.

Nevertheless, the works carried out so far allow to draw a hypothesis that the plant described in the article may in the future be a good medicine and a preventive measure against many diseases affecting our society.

Declarations

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Author contributions
Conceptualization, M.S. and M.Sz.; Writing – Original Draft Preparation, M.S. and M.Sz; Writing – Review & Editing, M.S. and M.Sz.

Conflicts of interest
The authors declare no conflict of interest.

Data availability
Data supporting the results of this study shall, upon appropriate request, be available from the corresponding author.

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