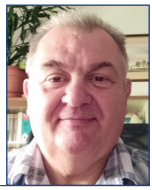
Potential applications and effects of silymarin in domestic animals – a review



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Abstract

Silymarin is a mixture of flavonolignan fractions from the medicinal plant milk thistle, which is primarily used as a hepatoprotector in humans and animals, and acts as an antioxidant, anti-inflammatory, antifibrotic, and antiapoptotic agent. As a dietary supplement, it is increasingly used to treat various liver diseases, some intoxications, prevent side effects of chemotherapy and protect the kidneys in dogs, birds, poultry, rabbits, cats, horses and other animals. The use of silymarin in dairy cows showed an improved biochemical profile of cows, reduced occurrence of ketosis and increased milk production. In pigs, nutrient digestibility, total average daily feed intake, and average daily weight gain improved, while in sport horses, silymarin supplementation accelerated the return of cortisol levels to pre-exercise levels. Lipidosis of the liver or fatty liver disease is a common disorder among captive parrots. After long-term administration of 100–150 mg/kg silymarin in food every 8–12 hours, the health condition improved significantly according to the testimonies of parrot owners and veterinarians. In intensive poultry production systems, silymarin is used in broilers as a hepatotonic, to improve carcass characteristics, to boost the immune system and intestinal health, and as a growth promoter, and in laying hens to improve egg quality. In addition, it mitigated the negative effects of mycotoxins in broilers, chickens and Japanese quails. Although numerous studies are known about the effect of milk thistle and silymarin, their use on animals is not yet widespread.

Key words: *application; exotic birds; domestic animals; milk thistle; pets; silymarin*

Introduction

Milk thistle (*Silybum marianum*, L. Gaertn.) is a member of the Asteraceae (Compositae) family, which includes the daisies, artichokes, sunflowers, thistles, etc. The plant was named for the milky veins on the broad and toothed leaves. The flower has a large purple flower head. Although milk thistle is one of the oldest and thoroughly researched medicinal plants in the treatment of liver diseases (Radko and Cybulski, 2007), Dioscorides (a Greek physician and botanist) originally used it in the first century AD as a medicine for snake bites, while in the sixteenth century it was used to treat jaundice and gallstones (Bauer Petrovska, 2012).

Fruits and seeds of milk thistle contain: 1.3-3% of flavonolignans (silibinin

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and isosilibinin, silicristin and silidianin), flavonoids (flavones: apigenin, chrysoeriol, eriodictyol, and flavonols: taxifolin, kaempferol, quercetin), 20-30% fatty oils (linoleic and oleic acids, palmitic, linolenic, behenic and others), 0.2-0.6% phytosterols (β-sitosterol), and other compounds (British Herbal Compendium, 2006; EMA, 2018). The active extract from dried fruits and seeds of milk thistle is silymarin, which has exceptional antioxidant, hepatoprotective, anti-inflammatory, immunomodulating, antidiabetic, antiapoptotic, and anti-amyloidogenic properties that have been proven in extensive clinical trials (Vargas-Mendoza et al., 2014; Surai, 2015; Saeed et al., 2017; Haddadi et al., 2020; Xiao et al., 2024). Silymarin is a mixture of flavonolignans such as silibinin or silybin (A and B), isosilibinin or isosilybin (A and B), silychristin, silydianin, taxifolin (small amount) and other polyphenolic compounds (Haddadi et al., 2020; Ranjan and Gautam, 2023; Jaffar et al., 2024). Milk thistle and its derivatives are classified as neutraceuticals, a term that denotes the pharmaceutical effect of a compound or food product for which there is no scientifically confirmed or approved clinical benefit. Today, there is more evidence that the active ingredient silymarin has benefits for a variety of liver and gallbladder disorders in humans and as a medicine for animals.

Pharmacokinetics and pharmacodynamics of silymarin

After an oral dose, the absorption of silibinin is low, as only 20-50% of crude silymarin extract is absorbed in the digestive tract (Fraschini et al., 2002). The lipophilic structure facilitates absorption in the digestive tract after dissolution in lipid-rich environments. Limited solubility in water affects its bioavailability since water is the primary medium for nutrient absorption. To improve its bioavailability, new formulations obtained by the technique of micronisation and complexation of phospholipids are used (Mihailović et al., 2023). A special combination of silymarin is administered orally in the form of capsules with a standard extract containing 70-80% silymarin. Silibinin (the main constituent of silymarin) takes 2-4 hours to reach its peak plasma concentration after consumption, with a plasma half-life of 6-8 hours (Zhu et al., 2013). All components of silymarin are absorbed into liver cells via the digestive tract, and undergo biotransformation processes (Tighe et al., 2020). Silibinin must be metabolised to be removed from the body through bile and faeces. About 80% of silibinin is eliminated as a water-soluble glucuronide and sulfate conjugate via bile, while 20–40% of bile containing silibinin conjugates is reabsorbed in the enterohepatic circulation. Urinary excretion is insignificant (3-8%). After a single dose, bile excretion starts 24 hours later.

The acute toxicity of silymarin is very low, and was studied after IV administration in mice and rats (385-400 mg/kg bw), rabbits and dogs (LD_{50} 140 mg/kg bw). Tolerance for slow IV infusion in rats was greater than 2 g/kg, and for oral administration over 10 g/kg body weight (Fraschini et al., 2002; Soleimani et al., 2019).

Effects of silymarin

Silymarin protects liver cells by significantly reducing oxidative stress, capturing free radicals, slowing or preventing fibrogenesis, stimulating the transcription of RNA polymerase I and rRNA enzymes, inhibiting the catalytic activity of cytochrome P450 isoenzymes, and inhibiting membrane transport proteins. It protects

healthy liver cells and those that have not yet been permanently damaged by significantly reducing oxidative stress, thereby mitigating cytotoxicity (Jaffar et al., 2024). In addition to slowing the development of liver disorders by trapping free radicals (superoxide, hydroxyl, hydrogen peroxide and lipid peroxide radicals implicated in liver diseases), silymarin has an anti-inflammatory effect and stimulates the regeneration of liver cells (Marmouzi et al., 2021). The chain reaction of lipid peroxidation damages the cell membrane and the oxidation of membrane lipids and proteins continues. Silymarin likely has a dual, antagonistic effect, i.e., by reducing the load of free radicals and by depleting the two main detoxification mechanisms by increasing the level of GSH and stimulating the activity of superoxide dismutase (SOD). It slows fibrogenesis, the development of cirrhosis and deposition of collagen fibres by transforming stellate hepatocytes into myofibroblasts (Gebhardt, 2002). In addition, silymarin enters the cell nucleus and stimulates the enzymes RNA polymerase I and rRNA transcription, leading to an increased formation of ribosomes, which in turn accelerates the synthesis of proteins and DNA (Sonnenbichler and Zetl, 1986). Also, silymarin inhibits the catalytic activity of cytochrome P450 isozymes *in vitro* in very high concentrations that are impossible to achieve in a living organism, thus confirming the harmlessness of the preparation. Finally, silymarin increases membrane stability against damage by inhibition of membrane transport proteins, so it can prevent the absorption of toxins into hepatocytes.

Extracts of many medicinal plants show inhibitory effects on the growth and proliferation of tumours, such as the extract of the plant *Santolina chamaecyparissus* L. reduced the frequency, size and number of breast cancer tumours in Wistar rats (Azevedo et al., 2024). Another example is the extract of *Cytinus hypocistis* (L.) subspecies *macranthus*, which had an antiproliferative effect on the development of human papillomavirus 16 in mice (Medeiros et al., 2023). Anticarcinogenic effects as well as the potential to reduce the growth of malignant formations have fasting without malnutrition associated with the hepatoprotective action of silymarin, which inhibits glycolysis, reduces glucose levels and induces external apoptosis and significantly slows the growth of hepatocellular carcinoma (Xiao et al., 2024). Numerous studies are known about the antitumour effects of silymarin in humans and animals (Agarwal et al., 2006; Forghani et al., 2014; Belli et al., 2017; Won et al., 2018). In addition, there is the potential of using silymarin in neurological and neurodegenerative disorders in humans due to its bioavailability in the brain and the application of nanotechnology (Ranjan and Gautam, 2023).

Side effects when using silymarin are rare, recorded in humans as nausea, vomiting, diarrhoea and skin allergies (Khazaei et al., 2022). In dogs, in a case of overdose with doses greater than 1.5 grams per day, it can cause diarrhoea due to increased bile flow. Due to the content of 0.2-0.6% phytosterols (β-sitosterol), certain unpurified preparations of milk thistle can affect the level of oestrogen, so such preparations should be used with caution in animals with hormonal disorders (Radko and Cybulski, 2007).

Use of silymarin in parrots, exotic birds, and poultry

Disorders such as hepatic lipidosis or fatty liver disease are highly prevalent in captive psittacines. In practice, there are many testimonies of veterinarians and parrot owners, who noticed that the

health of their pets improved significantly by introducing milk thistle into their diet after diagnosing liver lipidosis or fatty liver disease. Along with the treatment of fatty liver disease, supportive therapy and a change in diet, weight reduction of the affected bird is required. During and after the disease, milk thistle is increasingly used as a medicine for the treatment and prevention of recurrence and for the well-being of animals affected by these metabolic disorders and diseases. Milk thistle has been reported to have very low toxicity in most wild and domestic animals and humans. Suggested doses of silymarin in birds range from 50-250 mg/day depending on the purity and composition of various milk thistle products for human or animal use on the market. According to Carpenter, (2018), the dose for birds is 100-150 mg/kg every 8-12 hours. For example: Silymarin Belupo® (Belupo, Croatia) capsule contains 168.35-205.76 mg of *Silybum marianum* L. Gaertner fruit, which corresponds to 100 mg of silymarin (expressed as silibinin). The dose for a budgie (body weight about 50 grams) is half a capsule (Silymarin) sprinkled on the grain mixture they are fed with. In parrots, it is used in combination with L-carnitine, betaine, vitamin B_{12} or other hepatoactive compounds.

In intensive poultry production systems, silymarin can be used in broilers as a growth promoter, and in laying hens to improve the quantity and quality of eggs. It can be used as a hepatotonic and to improve the carcass characteristics of broiler chickens, to improve the immune system of poultry and intestinal health (Suchy et al., 2008; Alhidary et al., 2017; Abdalla et al., 2018; Baradaran et al., 2019; Abdulwahid and Oleiwi, 2021). Silymarin as a feed supplement for broilers had a positive effect on growth at the end of the production cycle, reducing oxidative stress, improving meat quality, increasing unsaturated fatty acids and mitigating the negative effects of mycotoxins (Armanini et al., 2021). Since silymarin contains many flavonolignans, it has antioxidant, anti-inflammatory, immune stimulating and stabilising effects on liver cells (Abd El-Ghany, 2022). Addition of silymarin to the diet of broiler Japanese quail mitigated the dangerous effects of aflatoxins (Khaleghipour et al., 2019).

Use of silymarin in ruminants, pigs and horses

In dairy cows, during the transition period and early lactation, metabolic disorders such as lipomobilisation syndrome, fatty liver and ketosis can occur. As the body tries to reduce the negative energy imbalance through the mobilisation of fat, a metabolic disorder often occurs that leads to the development of a fatty liver (Peša et al., 2016). The consequences of peripartum fatty liver can be alleviated by the use of silymarin. The number of cows with ketonuria decreased, the amount of milk increased by 3.4-7.7% and the biochemical profile improved in cows that received silymarin in a dose of only 10 g per day per cow (Tedesco et al 2004; Vojtisek et al., 1991).

The dietary supplement of 0.10% micelle silymarin in concentrate for pigs improved the overall average daily feed intake and average daily gain, enhanced the digestibility of dry matter nutrients and nitrogen, and had a positive effect on the gut microbiome (increased number of lactobacilli and reduced number of *E. coli*) in pigs during the fattening period (Hossain et al., 2024). Grela et al. (2020) showed that the finishing diet of pigs with 3% milk thistle seeds improved body growth, and Zhang and Kim (2022) showed that micelle silymarin supplementation up to 0.2% im-

proved body weight gain in finishing pigs. For the pharmacokinetics of silymarin in pigs, solid dispersion showed better results with rapid absorption and elimination after oral administration compared to premix, in accordance with previous data on the *in vitro* dissolution of silymarin (Xu et al., 2022).

In sport horses, administration of silymarin accelerated the return of cortisol to resting values before exercise (Dockalova et al., 2021; Tedesco and Guerrini, 2023).

Use of silymarin in dogs and cats

Milk thistle nutritional supplements for dogs and cats are available in three formulations as powder, capsules and liquids. The most commonly used formulation for dogs are chewable capsules, and they are classified as a dietary supplement. Various preparations of silymarin for dogs can be obtained on different markets, such as Denamarin, Hepatosupport, Hepatoprotect, Milk Thistle, Silymarin Advanced, Hepatoforce, BARF Silybum Marianum, and many others (Gogulski et al., 2020; Marchegiani et al., 2020). The active ingredient, silymarin, is extracted from the plant, so milk thistle medications approved for human use can be used in appropriate doses in dogs and cats. In dogs and cats, treatment with silymarin is aimed at acute and chronic liver diseases, in the detoxification process and supportive treatment in chemotherapy (Gogulski et al., 2021; Tedesco and Guerrini, 2023). The recommended dose of silymarin for dogs and cats is 20-50 mg/kg/day, *i.e.,* for the preparation Nutramax which contains silybin bound to phosphatidylcholine (for better absorption) a lower dose of 5-10 mg/kg/day is required.

Use of silymarin in other species

In addition to improving growth and food utilisation in some laboratory animals (Khazaei et al., 2022), silymarin is also recommended for common marmosets and rabbits at 4-15 mg/kg PO every 8 or 12 hours, and in rats at 50-200 mg/kg/day PO (Carpenter, 2018).

In reptiles, silymarin can mainly be used to control inflammation and limit toxin intake at a dose of 30-40 mg/kg up to three times a day PO. It is often used in turtles, but is not necessarily useful in hepatic lipidosis (Martínez Silvestre, 2018). The dosage and decision to use silymarin in reptiles should be carefully considered and prescribed by a reptile specialist.

Conclusions

Although numerous studies are known about the effects of the milk thistle plant and its derivatives, they are not yet wide applied in animals. Despite the great potential for the application of active substances from milk thistle, not only in alternative or complementary, but also in classical veterinary medicine, primarily in birds, dogs and other species from the human environment, caution is needed in the application of different forms or formulations of preparations on the market, and dosing to ensure the safety and well-being of domestic animals and pets.

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Mogućnosti primjena i učinaka silimarina na domaće životinje – pregledni rad

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Silimarin je mješavina flavonolignanskih frakcija iz ljekovite biljke sikavice koja se prije svega koristi kao hepatoprotektor u ljudi i životinja, a djeluje i kao antioksidans, protuupalno, antifibrotično, antilipidno i peroksidativno sredstvo. Kao dodatak prehrani silimarin se sve više koristi za liječenje raznih bolesti jetre, nekih intoksikacija; za sprječavanje nuspojava kemoterapije te za zaštitu bubrega u: pasa, ptica, peradi, kunića, mačaka, konja i drugih životinja. Primjena silimarina u mliječnih krava poboljšava biokemijski profil krava, smanjuje pojavu ketoze i povećava količinu proizvedenog mlijeka; u svinja se poboljšava probavljivost hranjivih tvari, ukupni prosječni dnevni unos hrane i prosječni dnevni prirast težine, a u sportskih konja dodatak silimarina ubrzava povratak razine kortizola na razine prije vježbanja. Lipidoza jetre ili bolest masne jetre vrlo je čest poremećaj u papiga u zatočeništvu, a nakon dugotrajne primjene 100-150 mg/kg silimarina u hrani svakih 8-12 sati, po svjedočanstvima vlasnika papiga i veterinara zdravstveno stanje se znatno popravilo. U sustavima intenzivne proizvodnje peradi silimarin se u brojlera koristi kao hepatotonik, za poboljšanje karakteristika trupa, za poboljšanje imunološkog sustava i zdravlja crijeva i kao pospješivač rasta, a u kokoši nesilica za poboljšanje kvalitete jaja. Silimarin je ublažio i negativne učinke mikotoksina u brojlera, pilića i japanskih prepelica. Iako se provode brojna istraživanja o učinku sikavice i silimarina, njihova široka primjena na životinjama još nije iskorištena.

Ključne riječi: *primjena, egzotične ptice, domaće životinje, sikavica, kućni ljubimci, silimarin*