

# DETOXIS

## Feed supplement for cats and dogs to support liver health and normal function

### DETOXIS<DÉ-TO-XIS

The name is inspired by the Latin words « de », which means « down/away from, off » and « toxicum » which means « poison »

*A Small Lexicon of Modern Latin: English-Latin Fundatio Melissa; 1988*

A premium combination of hepatoprotective and antioxidant ingredients to promote liver health in senior animals and support detoxification processes in animals with liver dysfunction. Acute and chronic hepatobiliary diseases are quite commonly reported in both dogs and cats<sup>1</sup>. Milk thistle (*Silybum marianum*) extract has a well-established pharmacological reputation for treatments of human liver disease, but it is also used in animals. Artichoke (*Cynara scolymus*) is well known in traditional medicine due to its beneficial effects in treatment of diseases of the biliary and digestive tracts. L-methionine is transformed in S-adenosylmethionine (S-AMe) which is a cytoprotective agent. Alpha-lipoic acid is associated with increasing glutathione activity, which is an important non-enzymatic defense of the liver.

### Milk thistle extract

The administration of milk thistle to animals as extract (feed additive) or as seed cake with the seed residue still containing the bioactive components (feed ingredient), is motivated by the complexity of silymarin registration as a veterinary drug<sup>2</sup>. In farm animals the drug improves the animals' performance and product quality and oxidative stability, supports liver function during productive life-cycle, improves gut-health and morphology, and can reduce intestinal pathogens. In dogs and cats, the treatment is focused on acute and chronic liver diseases including the detoxification processes and support of drug treatments including chemotherapy. In equine athletes seed cake showed positive effects and a faster return of cortisol to the resting values before exercise occurred.

A standard milk thistle extract contains 60% to 70% silymarin (SIL), which is composed of a mixture of flavonolignans, such as silybin, isosilybin, silydianin and silychristin, with silybin being the major active component. Silybin is a substance with proven liver-beneficial properties. Dietary supplementation with silybin seems a reasonable tool to support a core treatment for liver disease. The literature indicates that silybin acts not only as an antioxidant, but also as an antifibrotic agent and a stimulator of cell regeneration. Due to its multidirectional action, it can effectively reduce liver damage, or help prevent it and has been reported effective in laboratory animals, dogs, and humans. This was confirmed by an observational study<sup>3,4</sup> on a

total of 15 dogs with diagnosed liver conditions, who were supplemented with silybin at a dose of 28.3 mg silybin per 10 kg BW for 30 days. Significant improvements were reported in the liver blood markers after the supplementation period. Another study<sup>5</sup> suggests that a combination of S-adenosylmethionine and silybin can minimize increased liver enzyme activity during chemotherapy in cancer treatment in dogs.

Unlike dogs, cats are extremely sensitive to the toxic effects of several molecules because of their hepatic enzyme deficiency, in particular the glucuronyl transferases. However, this relative deficiency of the glucuronide conjugation pathway results in more drugs being conjugated to sulfates, but the sulfation pathway has a finite capacity in cats, which is also lower than in other species. At a dose of 30 mg/kg BW, SIL had the same effect as N-acetylcysteine in the treatment of liver damage from acetaminophen intoxication in cats. In SIL treated cats, the levels of ALT, AST, LDH, methemoglobin and bilirubin did not increase as they did in cats given acetaminophen alone<sup>6</sup>.

Generally, silybin administration should be considered as a supportive therapy in liver diseases.

#### Artichoke extract

Native to the Mediterranean Basin, artichoke is cultivated all over the world for edible and medicinal purposes. Its bioactive components, present mainly in the leaves rather than in the artichoke heads, include mono- and dicaffeoylquinic acids (e.g., chlorogenic acid and cynarin) and flavonoids (e.g., luteolin, apigenin, and their glucosides and rutinosides). Antioxidative, hepatoprotective, bile expelling, and lipid-lowering effects have been associated with the artichoke leaf extract<sup>7</sup>.

A review of existing literature<sup>8</sup> revealed that artichoke supplementation significantly reduces AST and ALT in patients with non-alcoholic fatty liver disease and ALT among overweight/obese subjects. These results are in accord with the meta-analysis of animal studies (23, mainly rats)<sup>9</sup> where the authors pointed out that artichoke extract supplementation had beneficial effect on antioxidant balance (increase superoxide dismutase, catalase, GSH, and glutathione peroxidase levels and decrease malondialdehyde level in liver and plasma) in animals with induced liver disease compared with others.

#### L-methionine

S-adenosylmethionine (SAME) is the hepatoprotective derivative of L-methionine and is generated from L-methionine and ATP in a two-step reaction catalyzed by methionine adenosyl transferase (MAT)<sup>10</sup>. MAT activity is decreased in many types of liver disease, requiring exogenous administration of SAME. Unfortunately, S-

adenosylmethionine (S-AdoMet) is not authorized in EU for use in feed, so the precursor (L-methionine) is used instead.

Oral S-AdoMet administration has been evaluated in healthy cats and dogs. Normal dogs and cats given 20 mg/kg and 30 to 50 mg/kg orally, respectively, had significantly increased plasma S-AdoMet concentration, increased hepatic GSH (glutathione) levels, and no overt signs of toxicity<sup>11,12</sup>. Oral S-AdoMet administration ameliorated acetaminophen-induced red blood cell and hepatic damage in cats (85 mg/kg for 3 days followed by 40 mg/kg) and dogs (40 mg/kg followed by 20 mg/kg), respectively<sup>13,14</sup>. In a study of prednisolone treated dogs, oral S-AdoMet (20 mg/kg) did not prevent the development of hepatic vacuolar changes or the induction of serum hepatic enzyme activity but increased hepatic GSH levels<sup>12</sup>.

### Alpha-Lipoic acid

Lipoic acid can function as an antioxidant in virtually all tissues and therefore may be referred to as a universal antioxidant or the antioxidant of antioxidants<sup>15</sup>. In a study of alpha-lipoic acid on the glutathione status in healthy adult dogs, a significant increase was observed for GSH, GSSG and total glutathione in RBC lysate at month 6<sup>16</sup>. In a study in cats on the effects of dietary antioxidant supplementation before and after oral acetaminophen challenge, alpha-lipoic acid did not act as an antioxidant but appeared to enhance oxidant effects of acetaminophen<sup>17</sup>.

### Vitamin C

In most domestic species, the ability to synthesize vitamin C is present during the first weeks of postnatal life, with primary biosynthesis from D-glucose occurring in the liver of both dogs and cats<sup>18</sup>. Since vitamin C is hepatically synthesized, the vitamin is considered nonessential from a dietary perspective for these species.

Several studies in veterinary medicine have evaluated vitamin C levels in animals with disease states associated with increased oxidative stress<sup>19</sup>. Vitamin C has been recommended to prevent oxidative damage from consumption of propylene glycol or onion powder in cats<sup>20</sup> as well as to treat methemoglobinemia secondary to acetaminophen toxicosis<sup>21</sup>. However, the evidence for these recommendations is lacking.

In a study conducted on high-fat-diet-induced mice, prophylactic use of low (15 mg/kg per day) and medium (30 mg/kg per day) doses of Vitamin C reduced the risk of Steatohepatitis (NASH) development, as evidenced by the significantly decreased weight of the body, adipose tissue mass, and steatosis<sup>22</sup>.

### Vitamin B6 & Vitamin B12

Because they are water-soluble, most B vitamins are not stored in the body to a great extent. However, B vitamins are involved as cofactors in numerous metabolic

reactions, including hepatic metabolism of macronutrients. B vitamins should be provided in the diet of patients who are eating a sufficient quantity of food, or they can be supplied parenterally if necessary. For patients with liver disease, prolonged anorexia or hyporexia (if present) and reduced hepatic metabolic capacity make adequate intake of B vitamins essential<sup>23</sup>.

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