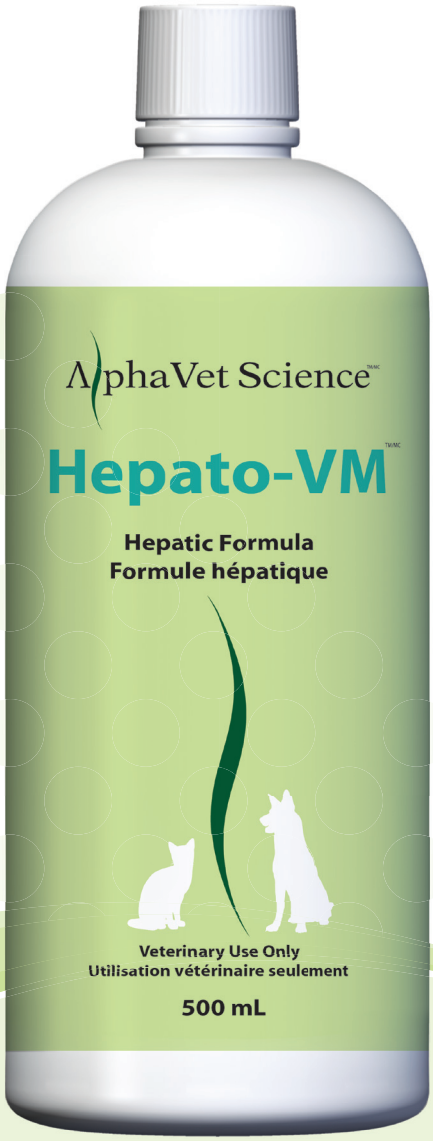
AlphaVet Science™/MC



Just Natural Science™

La science au naturel, simplement™

AlphaVet Science™

Hepato-VM™

Hepato-VM™ supports normal function and health of the liver. Medicinal herbs used in Hepato-VM™ provide a rich source of antioxidants that are important for normal liver function.

INDICATIONS
- Hepatic detoxification

INGREDIENTS ACTIONS
- Anticholesterolemic
- Anti-inflammatory
- Antioxidant
- Cholagogue
- Choleretic
- Depurative
- Hepatic trophorestorative
- Hepatoprotective
- Laxative
- Stomachic

ADMINISTRATION Oral

DOSAGE

1-10 lbs	2.5 mL (½ teaspoon) daily.
11-20 lbs	5 mL (1 teaspoon) daily.
21-50 lbs	7.5 mL (1½ teaspoons) daily.
51-100 lbs	10 mL (2 teaspoons) daily.
> 100 lbs	15 mL (1 tablespoon) daily.

STORAGE Store in a cool dry place and away from direct sunlight. Keep bottle cap tightly closed when not in use.

PACKAGING 500 mL/bottle

Hepato-VM™ FORMULA

1 teaspoon (5 mL) contains:

Milk Thistle Fruit	(*Silybum marianum*/Fructus Silybi Mariae)	150 mg
Dandelion Root	(*Taraxacum officinale*/Radix Taraxaci)	120 mg
Capillary Artemisia Herb	(*Artemisia capillaries*/Herba Artemisiae Capillaris)	100 mg
Chanca Piedra Herb	(*Phyllanthus niruri*/Herba Phyllanthi)	75 mg
Chinese Thoroughwax Root	(*Bupleurum chinense*/Radix Bupleuri)	75 mg
Picrorhiza Rhizome	(*Picrorhiza kurroa*/Rhizoma Picrorhizae)	75 mg
Chinese Magnoliavine Fruit	(*Schisandra chinensis*/Fructus Schisandrae)	50 mg
Greater Burdock Root	(*Arctium lappa*/Radix Bardanae)	50 mg
Holy Basil Leaf	(*Ocimum sanctum*/Folium Ocimi Sancti)	50 mg

NON-MEDICINAL INGREDIENTS

Stevia, Citric acid, Potassium sorbate, Purified water, Sodium benzoate.

Hepato-VM™ is manufactured under strict GMP standards and contains no dairy, yeast, corn, wheat or gluten. Does not contain animal by-products.

Silybum marianum (Milk Thistle)

Fructus Silybi Mariae consists of the dried ripe fruits, freed from the pappus of *Silybum marianum*. It is used as a supportive treatment of acute or chronic hepatitis and cirrhosis induced by drugs or toxins (WHO, 2004). The major active constituents of Fructus Silybi Mariae are flavonolignans, collectively known as silymarin and its hepatoprotective effects are accomplished via several mechanisms including antioxidation, inhibition of lipid peroxidation, increased liver detoxification via inhibition of Phase I detoxification, enhanced glucuronidation, and protection of glutathione depletion (Saller *et al.*, 2001; Twedt, 2010). Silymarin has also been shown to increase hepatocyte protein synthesis, thereby promoting hepatic tissue regeneration. Animal studies have demonstrated silybin, an active steroisomer, to reduce the conversion of hepatic stellate cells into myofibroblasts, slowing or even reversing fibrosis (AMR, 1999). In two clinical trials of dogs given hepatotoxic *Amanita phalloides*, silymarin improved the biochemical and histologic measure of hepatotoxicity, and survival was improved (Wynn, 2006).

TOXICOLOGY

Toxicity for Fructus Silybi Mariae has not been documented in dogs and cats when administered orally in therapeutic doses. The maximum tolerated oral dose of silymarin in dogs, (a mixture of flavonlignans extracted from Fructus Silybi Mariae) was calculated to be about 300 mg/kg of body weight (Desplaces *et al.*, 1975). The oral LD_{50} of silymarin in rats was 10,000 mg/kg of body weight (Abascal & Yarnell, 2003). In acute toxicity studies of silymarin after intravenous infusion, the LD_{50} values were 400 mg/kg of body weight in mice, 385 mg/kg of body weight in rats and 140 mg/kg of body weight in rabbits and dogs though these values may vary depending on infusion rate. With slow infusion over 2 to 3 hours the LD_{50} was 2 g/kg of body weight in rats (Ghosh *et al.*, 2010).

Equivalent toxic dose in 20 kg dog: 200,000 mg PO of silymarin.
Equivalent toxic dose in 5 kg cat: 50,000 mg PO of silymarin.

DRUG INTERACTIONS

Validated interactions studies do not exist for Fructus Silybi Mariae preparations. Clinical interactions with other drugs have not been reported.

Silymarin has been shown to reduce the activity of the enzyme CYP3A4 *in vitro* and may impair hepatic metabolism of certain co-administered drugs in humans (Venkataramanan *et al.*, 2000). However, another *in vivo* human study indicated that silymarin does not exhibit CYP3A4 inhibition effect (Fuhr *et al.*, 2007).

Taraxacum officinale (Dandelion)

Radix Taraxaci is one of the strongest cholagogues and choleretics known. Its ability to promote the flow of bile is unequaled among the common herbs (WHO, 2007; Vogel, 1977). The European Scientific Cooperative on Phytotherapy (ESCOP) recommends Radix Taraxaci for restoration of hepatic and biliary function, dyspepsia, and anorexia. The German Commission E authorizes the use of formulations containing Radix Taraxaci and Folium Taraxaci for biliary abnormalities, appetite loss, dyspepsia, and for stimulation of diuresis. In alcohol-induced hepatotoxicity, Radix Taraxaci extract was found to reduce serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and lactate dehydrogenase activities and significantly increase hepatic antioxidant activities, including catalase, glutathione-S-transferase, glutathione peroxidase, glutathione reductase, and glutathione (You *et al.*, 2010).

TOXICOLOGY

Toxicity for Radix Taraxaci has not been documented in dogs and cats when administered orally in therapeutic doses. No visible signs of acute toxicity were observed after oral administration of dried Radix et Herba Taraxaci at 3-6 g/kg of body weight in rats. Different types of extracts demonstrated very low toxicity: Herba et Radix Taraxaci fluid extract, intraperitoneal LD_{50} 28.8 and 36.6 g/kg of body weight, respectively, in mice. Ethanol extracts of Radix et Herba Taraxaci showed very low toxicity up to doses of 10 g/kg PO and 4 g/kg intraperitoneal in rats and mice (EMA, 2009).

Equivalent toxic dose in 20 kg dog: 200 g PO of Radix et Herba Taraxaci ethanol extract.
Equivalent toxic dose in 5 kg cat: 50 g PO of Radix et Herba Taraxaci ethanol extract.

DRUG INTERACTIONS

Validated interactions studies do not exist for Radix et Herba Taraxaci preparations. Clinical interactions with other drugs have not been reported. However, Radix et Herba Taraxaci may potentiate the action of other diuretics and may interfere with hypoglycaemic therapy (Newall *et al.*, 1996).

Artemisia capillaris (Capillary Artemisia)

Herba Artemisiae Capillaris is an effective remedy for liver problems, being specifically helpful in treating liver diseases such as hepatitis, fatty liver, cirrhosis of the liver and jaundice. In dogs with chronic gallbladder fistulae, oral administration (0.3 g/kg/day) of scoparone, an active constituent of Herba Artemisiae Capillaris, increased the production of bile by a mean of 73.86% in 3 h (Chen & Chen, 2004; Zhu, 1998). The active constituents scoparone, artepillin A, capillartemisin B, and artepillin have exhibited choleretic activity in vivo (Okuno *et al.*, 1998). In studies in obese animals, Herba Artemisiae Capillaris was found to be effective in strengthening the antioxidant defence system, reducing the generation of reactive oxygen species and damaging oxidative substances in the liver (Hong & Lee, 2009). Herba Artemisiae Capillaris and Rhizoma Picrorhizae mixtures have shown good synergic hepatoprotective activity that was attributed to increasing free-radical scavenging ability (Lee *et al.*, 2008). Herba Artemisiae Capillaris extract demonstrates anti-inflammatory activity by inhibiting the expression of inflammatory proteins such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and tumor necrosis factor-alpha [TNF-alpha] (Hong *et al.*, 2004).

TOXICOLOGY

Toxicity for Herba Artemisiae Capillaris has not been documented in dogs and cats when administered orally in therapeutic doses. The acute LD_{50} of capillin, an active constituent of Herba Artemisiae Capillaris in mice was 6.98 mg/kg of body weight. In rats receiving oral administration of 50,200 and 400 mg/kg of body weight of p-hydroxyacetophenone, an active constituent of Herba Artemisiae Capillaris, for 3 months, no significant changes were found in the blood and organ functions. The intraperitoneal LD_{50} values of p-hydroxyacetophenone were 0.5 g/kg of body weight in mice and 2.2 g/kg of body weight in rats (Chen & Chen, 2004). The LD_{50} for capillarin in mice is 262.5 mg/kg of body weight via intraperitoneal injection (Zhu, 1988).

Equivalent toxic dose in 20 kg dog: 5,310 mg IP of capillarin.
Equivalent toxic dose in 5 kg cat: 1,313 mg IP of capillarin.

DRUG INTERACTIONS

Validated interactions studies do not exist for Herba Artemisiae Capillaris preparations. Clinical interactions with other drugs have not been reported.

Phyllanthus niruri (Chanca Piedra)

Herba Phyllanthi extract has been used extensively in the treatment of liver ailments in traditional medicine and its actions are attributed to its antioxidant and anti-inflammatory effects (Manjrekar *et al.*, 2008). The hepatoprotective activity of Herba Phyllanthi is due to the high phenolic and flavonoid content (Jain & Singhai, 2011). Phyllanthin, the principle constituent has been found to restore the level of total glutathione, and increase the activities of superoxide dismutase and glutathione reductase in hepatocyte injury in experimental studies (Chirdchupunseree & Pramyothin, 2010). In animal models, Herba Phyllanthi normalized carbon tetrachloride induced hepatotoxicity via its antioxidant properties by elevating the levels of superoxide dismutase and catalase in the liver (Bhattacharjee & Sil, 2007). In acetaminophen and nimesulide induced oxidative stress in the liver, the antioxidant activity of Herba Phyllanthi was comparable to that of vitamin E *in vivo* (Chatterjee & Sil, 2006; Bhattacharjee & Sil, 2006). A review of sixteen randomised clinical trials in patients with chronic hepatitis B virus infection reported that treatment with Herba Phyllanthi in combination with an antiviral drug was more effective than the antiviral drug alone (Xia *et al.*, 2011).

Note:

Phyllanthus niruri is also an ingredient in Nephro-VM™. Herba Phyllanthi has shown an inhibitory effect on calcium oxalate crystal growth and aggregation and may be beneficial in the prevention of urolithiasis.

TOXICOLOGY

Toxicity for Herba Phyllanthi has not been documented in dogs and cats when administered orally in therapeutic doses. The extract of Herba Phyllanthi is non-toxic having oral LD_{50} > 5 g/kg of body weight in mice (Evi *et al.*, 2008).

Equivalent toxic dose in 20 kg dog: >100 g PO of Herba Phyllanthi.
Equivalent toxic dose in 5 kg cat: >25 g PO of Herba Phyllanthi.

DRUG INTERACTIONS

Validated interactions studies do not exist for Herba Phyllanthi preparations. Clinical interactions with other drugs have not been reported. However, Herba Phyllanthi may potentiate insulin and anti-diabetic drugs due to its hypoglycemic effect (Brinker, 1998).

Bupleurum chinense (Chinese Thoroughwax)

The saikosaponins in Radix Bupleuri are mainly responsible for its medicinal activities. Saikosaponin A has been found to improve hepatic antioxidant capacity by increasing hepatic superoxide dismutase activity and total glutathione level. Saikosaponin A suppressed inflammation and fibrogenesis in chemically induced liver injury by reducing collagen deposition, inhibiting nuclear factor-kappa B expression and by increasing anti-inflammatory cytokine interleukin-10 (Wu *et al.*, 2010). Saikosaponin A has also demonstrated hepatoprotective effects by attenuating hepatic lipids and lipid peroxidation and enhancing antioxidant defence (Wu *et al.*, 2008). Saikosaponins also exert anti-inflammatory effects by inhibiting arachidonic acid metabolism *in vitro* and *in vivo* (Bermejo *et al.*, 1998).

TOXICOLOGY

Toxicity for Radix Bupleuri has not been documented in dogs and cats when administered orally in therapeutic doses. Aqueous extract of Radix Bupleuri did not show any toxic effects in rats and mice at oral doses of 6 g/kg of body weight (Mills & Bone, 2000). The LD_{50} in mice is 1.19 g/kg of body weight via intraperitoneal injection for essential oil of Radix Bupleuri, and 1.906 g/kg of body weight for saikosaponin, an active constituent of Radix Bupleuri (Chen & Chen, 2004).

Equivalent toxic dose in 20 kg dog: 38 g IP of saikosaponin.
Equivalent toxic dose in 5 kg cat: 9.5 g IP of saikosaponin.

DRUG INTERACTIONS

Validated interactions studies do not exist for Radix Bupleuri preparations. Clinical interactions with other drugs have not been reported.

Picrorhiza kurroa (Picrorhiza)

Rhizoma Picrorhizae is a distinguished medicinal herb of the Ayurvedic medicinal system, used mainly for the treatment of a variety of liver ailments. The major biologically active constituents are iridoid glycosides, cucurbitacin triterpenes and simple phenols (WHO, 2009). The iridoid glycoside mixture kutkin (picroside and kutkoside) isolated from Rhizoma Picrorhizae has shown significant hepato-protective efficacy in animal models of galactosamine, paracetamol, thioacetamide and carbon tetrachloride induced hepatic damage. It has also exhibited anti-viral and immune-stimulant activities (Verma *et al.*, 2009). The mechanism of action of Rhizoma Picrorhizae extract in liver protection involves kutkin, which can increase the activity rates of nucleolar polymerase A, leading to increased protein synthesis and subsequent enhanced regenerative ability. Kutkins scavenge free radicals and guard hepatocytes from the damage caused by lipid peroxidation through antioxidant activity. Apocynin, another active constituent of Rhizoma Picrorhizae, is a strong nicotinamide adenine dinucleotide phosphate-oxidase inhibitor and has shown anti-inflammatory properties. The mechanism of action of kutkins appears to be the same as that of silymarin, a hepato-protective constituent of *Silybum marianum* (Vaidya *et al.*, 1996).

TOXICOLOGY

Toxicity for Rhizoma Picrorhizae has not been documented in dogs and cats when administered orally in therapeutic doses. In mice, the LD_{50} for aqueous ethanol extract of Rhizoma Picrorhizae is 1.09 g/kg of body weight intraperitoneal, indicating low toxicity (Dhar *et al.*, 1973). The LD_{50} for 70% methanol extract of Rhizoma Picrorhizae in mice is >2 g/kg of body weight intragastrically (Lee, 1982). In rats, the LD_{50} of kutkin, an active constituent of Rhizoma Picrorhizae, is >2,600 mg/kg of body weight (CSIR, 1989-1990).

Equivalent toxic dose in 20 kg dog: 21.8 g IP of Rhizoma Picrorhizae ethanol extract.
Equivalent toxic dose in 5 kg cat: 5.45 g IP of Rhizoma Picrorhizae ethanol extract.

DRUG INTERACTIONS

Validated interactions studies do not exist for Rhizoma Picrorhizae preparations. Clinical interactions with other drugs have not been reported.

Schisandra chinensis (Chinese Magnoliavine)

Schisandrin B is a hepatoprotective ingredient isolated from Fructus Schisandrae, a traditional Chinese herb clinically used to treat viral and chemical hepatitis (Chiu & Ko, 2004). Animal studies have suggested that the mechanism of hepatoprotection of Fructus Schisandrae may involve the enhancement of mitochondrial glutathione antioxidant status and is attributed to schisandrin B (Chiu *et al.*, 2003). Animal studies also suggest Fructus Schisandrae may protect the liver from toxic damage, improve liver function, and stimulate liver cell regrowth (Bao *et al.*, 1980).

Note:

Schisandra chinensis is also an ingredient in Nephro-VM™. Schisandrol B, an active constituent of Fructus Schisandrae, enhances renal mitochondrial antioxidant status.

TOXICOLOGY

Toxicity for Fructus Schisandrae has not been documented in dogs and cats when administered orally in therapeutic doses. Acute toxicity tests have shown that ethanol extract of Fructus Schisandrae is relatively non-toxic, with an intragastric LD_{50} value of 35.63 ± 6.46 g/kg of body weight in mice (Pan *et al.*, 2011).

Equivalent toxic dose in 20 kg dog: 713 g IG of Fructus Schisandrae ethanol extract.
Equivalent toxic dose in 5 kg cat: 178 g IG of Fructus Schisandrae ethanol extract.

DRUG INTERACTIONS

Validated interactions studies do not exist for Fructus Schisandrae preparations. Clinical interactions with other drugs have not been reported. However, Fructus Schisandrae has been shown to inhibit CYP3A in an animal study (Lai *et al.*, 2009) and may affect the intracellular concentration of drugs metabolized by this enzyme.

Arctium lappa (Greater Burdock)

Radix Bardanae is one of the foremost detoxifying botanicals in both Chinese and Western herbal medicine. The hepatoprotective mechanism of Radix Bardanae could be attributed, at least in part, to its antioxidative activity, which decreases the oxidative stress on hepatocytes (Lin *et al.*, 2002). Arctigenin an active constituent of Radix Bardanae has demonstrated hepatoprotective properties through anti-inflammatory activity by suppressing the overproduction of nitric oxide and through down-regulation of iNOS expression and iNOS enzymatic activity (Zhao *et al.*, 2009). In animal models, Radix Bardanae protected the liver from carbon tetrachloride- and acetaminophen-induced damage through its antioxidant action by increasing glutathione and decreasing malondialdehyde levels in hepatocytes (Lin *et al.*, 2000).

TOXICOLOGY

Arctium lappa

Toxicity for Radix Bardanae has not been documented in dogs and cats when administered orally in therapeutic doses. LD_{50} for Radix Bardanae has not been determined.

DRUG INTERACTIONS

Validated interactions studies do not exist for Radix Bardanae preparations. Clinical interactions with other drugs have not been reported. However, an excessive dose of Radix Bardanae may interfere with hypoglycaemic therapy (Newall *et al.*, 1996).

Ocimum sanctum (Holy Basil)

Folium Ocimi Sancti is traditionally used for its hepatoprotective effect. Folium Ocimi Sancti has been shown to reduce hepatic cholesterol and triglyceride accumulations and increases fecal bile acid excretion. Folium Ocimi Sancti modulates the liver enzymatic antioxidants superoxide dismutase, catalase, glutathione-S-transferase, non-enzymatic antioxidants (reduced glutathione), lipid peroxidation end product, and malondialdehyde levels (El-safty, 2011). The exact mechanism of the hepatoprotective action of Folium Ocimi Sancti extract is not yet known. Its antioxidant activity seems to be the most important mode of its hepatoprotective action (Ubaid *et al.*, 2003). In drug-induced liver damage, extracts of Folium Ocimi Sancti exhibits significant hepatoprotective activity and synergism with Fructus Silybi Mariae (Lahon & Das, 2011).

Note:

Ocimum sanctum is also an ingredient in Immunine-VM™ and Pulmo-VM™. The immunomodulatory effects Folium Ocimi Sancti is attributed to its anti-stress properties. Folium Ocimi Sancti has been also shown to increase lung vital capacity and protect against bacterial colonization in the lungs.

TOXICOLOGY

Toxicity for Folium Ocimi Sancti has not been documented in dogs and cats when administered orally in therapeutic doses. The LD_{50} for fixed oil of Folium Ocimi Sancti was calculated at 42.5 mL/kg of body weight and long-term use of oil at 3 mL/kg of body weight does not produce any adverse effects in rats (Singh *et al.*, 2007). The LD_{50} of ethanol extract of Folium Ocimi Sancti in adult mice was found to be 4.5 g/kg of body weight oral and 3.2 g/kg of body weight intraperitoneal (Rahman *et al.*, 2011).

Equivalent toxic dose in 20 kg dog: 90 g PO of Folium Ocimi Sancti ethanol extract.
Equivalent toxic dose in 5 kg cat: 22.5 g PO of Folium Ocimi Sancti ethanol extract.

DRUG INTERACTIONS

Validated interactions studies do not exist for Folium Ocimi Sancti preparations. Clinical interactions with other drugs have not been reported.

SAFETY INFORMATION

PRECAUTIONS

- An examination from a veterinarian is recommended prior to using this product.
- Safe use in pregnant animals or animals intended for breeding has not been proven.
- If animal's condition worsens or does not improve, stop product administration and consult your veterinarian.
- Not to be used one week prior to surgery.
- Consult your veterinarian for potential drug interactions.
- Off-label use of this product in ruminants is not recommended.
- Oral use only.
- Administer during or after the animal has eaten to reduce incidence of gastrointestinal upset.
- Shake well before use.

WARNINGS

- To be used in dogs and cats only.
- Keep out of reach of children and animals.
- In case of accidental overdose, contact a health professional immediately.

ADVERSE REACTIONS

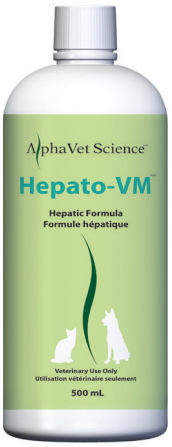
- Mild gastrointestinal discomfort may occur which is dose dependent.
- Can cause loose stools when administered frequently or in large amounts.

CONTRAINDICATIONS

- Contraindicated in pregnant and nursing dogs and cats.
- Contraindicated in obstruction of the biliary or intestinal tract.
- Contraindicated in acute gallbladder inflammation.

AlphaVet Science™

Hepato-VM™



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