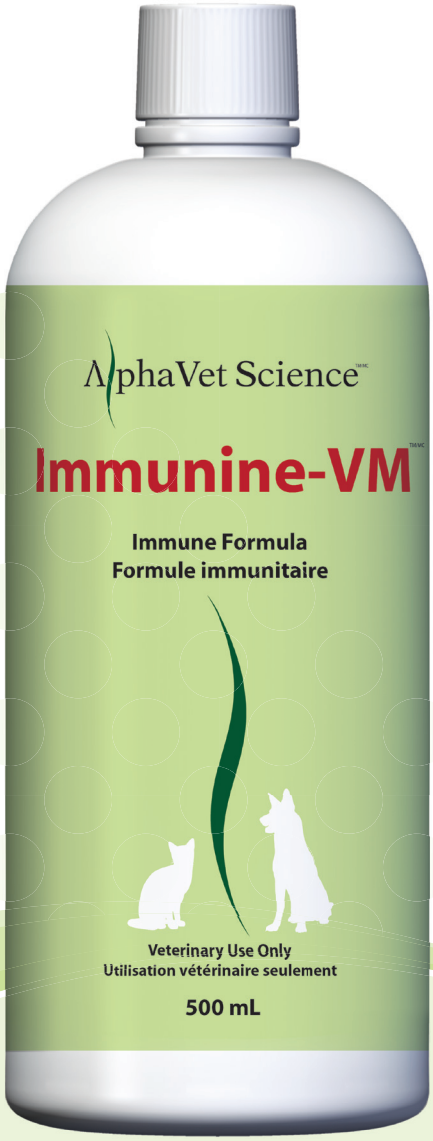
AlphaVet Science™/MC



Just Natural Science™

La science au naturel, simplement™

AlphaVet Science™

Immunine-VM™

Immunine-VM™ is specifically formulated with biological response modifying herbs containing antioxidant properties which help to maintain normal immune system function and reduce the negative effects of stress.

INDICATIONS
- Immune modulation
- Stress management

INGREDIENTS ACTIONS
- Adaptogenic
- Anti-fatigue
- Anti-stress
- Immunostimulant

PACKAGING 500 mL/bottle

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.

Immunine-VM™ FORMULA

1 teaspoon (5 mL) contains:

Reishi Mushroom	(*Ganoderma lucidum*/Ganoderma)	250 mg
Astragalus Root	(*Astragalus membranaceus*/Radix Astragali)	200 mg
Narrow-Leaf Echinacea Root	(*Echinacea angustifolia*/Radix Echinaceae)	200 mg
Uña de gato Bark	(*Uncaria tomentosa*/Cortex Uncariae)	150 mg
Ashwagandha Root	(*Withania somnifera*/Radix Withaniae)	100 mg
Eleuthero Root	(*Eleutherococcus senticosus*/Radix Eleutherococci)	100 mg
Chinese Privet Fruit	(*Ligustrum lucidum*/Fructus Ligustri Lucidi)	75 mg
Chinese Tinospora Stem	(*Tinospora sinensis*/Caulis Tinosporae)	75 mg
Holy Basil Leaf	(*Ocimum sanctum*/Folium Ocimi Sancti)	75 mg

NON-MEDICINAL INGREDIENTS

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

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

Ganoderma lucidum (Reishi Mushroom)

The "Miraculous King of Herbs" – Ganoderma, is highly regarded for its medicinal properties in the Far East and has unique properties that contribute much to the strengthening of the immune system. A number of reports have demonstrated that Ganoderma polysaccharides modulate immune function both *in vivo* and *in vitro*. The immunomodulating effects of Ganoderma polysaccharides are extensive, including promoting the function of antigen-presenting cells, the mononuclear phagocyte system, humoral immunity, and cellular immunity (Lin, 2005). The basidiocarp, mycelia and spores of *Ganoderma lucidum* contain approximately 400 different bioactive compounds, which mainly include triterpenoids, polysaccharides, nucleotides, sterols, steroids, fatty acids, proteins/peptides and trace elements which have been reported to have a number of pharmacological effects (Sanodiya *et al.*, 2009).

TOXICOLOGY

Toxicity for Ganoderma has not been documented in dogs and cats when administered orally in therapeutic doses. Oral LD_{50} of Ganoderma spore powder is >21.5 g/kg of body weight in mice (FDA, 1999). Oral LD_{50} of Ganoderma polysaccharides is >5 g/kg of body weight in mice (Li *et al.*, 2011).

Equivalent toxic dose in 20 kg dog: >430 g PO of Ganoderma spore powder.
Equivalent toxic dose in 5 kg cat: >107.5 g PO of Ganoderma spore powder.

DRUG INTERACTIONS

Validated interactions studies do not exist for Ganoderma preparations. Clinical interactions with other drugs have not been reported. However, caution is advised for those receiving immunosuppressive therapies as Ganoderma potentiates the immune system. The inhibition of platelet aggregation by Ganoderma may present an additive effect on anticoagulants (Wasser, 2005).

Astragalus membranaceus (Astragalus)

Radix Astragali has been valued by traditional Chinese medicine for its ability to enhance the immune system, and for its anti-stress and antimicrobial properties (Tan & Vanitha, 2004). Both *in vitro* and *in vivo* investigations have confirmed that Radix Astragali enhances the immune system through immunomodulation and immunorestorative effects (Cho & Leung, 2007). In immunosuppressed animal models, Radix Astragali exhibited immunoregulatory effect through elevating interleukin-2, interferon-gamma and the ratio of CD4+ and CD8+ T-lymphocytes (Luo *et al.*, 2009). The active constituents of Radix Astragali, icariin and astragalosid 1 accelerated the proliferation and differentiation of canine bone marrow stromal cells *in vitro* (Liu *et al.*, 2006). In a study for repairing alveolar bone defects in dogs, Radix Astragali showed alveolar bone generation and cementum regeneration (Xu *et al.*, 2007). In another experimental study, extracts of Radix Astragali showed a definite protective effect on the ischemic reperfusion of injured kidney in dogs (Yuan *et al.*, 2003).

TOXICOLOGY

Toxicity for Radix Astragali has not been documented in dogs and cats when administered orally in therapeutic doses. In dogs, Radix Astragali was found to be safe and without any side effects in a subchronic toxicity study. The safety dosage range was 2.85-19.95 g/kg of body weight (Yu *et al.*, 2007). LD_{50} of Radix Astragali intraperitoneal is 40 g/kg of body weight in mice (Chang & But, 1987).

Equivalent toxic dose in 20 kg dog: 800 g IP of Radix Astragali.
Equivalent toxic dose in 5 kg cat: 200 g IP of Radix Astragali.

DRUG INTERACTIONS

Validated interactions studies do not exist for Radix Astragali preparations. Currently there is no evidence of drug interactions resulting from the effects of Radix Astragali on drug-metabolizing systems (Stargrove *et al.*, 2008).

Echinacea angustifolia (Narrow-Leaf Echinacea)

One of the main mechanisms of action of *Echinacea angustifolia* is that it simulates phagocytosis in the blood stream. No single constituent has been found to be primarily responsible for Echinacea's immune-stimulating effect; rather they appear to all work together to accomplish this (AMR, 2001). The immune-stimulant effect is brought about by three mechanisms: activation of phagocytosis and stimulation of fibroblasts; increasing respiratory activity; and causing increased mobility of the leukocytes (WHO, 1999). It has been reported that chicoric acid, an active constituent of Radix Echinaceae has properties that include immunostimulation, phagocytosis, and anti-hyaluronidase activity (Pellati *et al.*, 2004). The lipophilic amides, alkamides and caffeic acid derivatives of Radix Echinaceae appear to contribute to the immunostimulant activity by stimulating phagocytosis of polymorphonuclear neutrophil granulocytes. High molecular weight polysaccharides of the aqueous extracts of Radix Echinaceae, including heteroxylan were found to activate phagocytosis and arabinogalactan promoted the release of tumour necrosis factor and the production of interleukin-1 and interferon beta when taken orally (WHO, 1999).

An open multi-centered veterinary clinical trial conducted by veterinarians in Switzerland found Radix Echinaceae as a well-tolerated alternative treatment of canine upper respiratory tract infections (Reichling *et al.*, 2003). Radix Echinaceae has been used to treat endoparasites and stomach problems in dogs and cats (Lans *et al.*, 2007).

TOXICOLOGY

Toxicity for Radix Echinaceae has not been documented in dogs and cats when administered orally in therapeutic doses. Oral LD_{50} of Radix Echinaceae is 2,500 mg/kg of body weight in mice. Intravenous LD_{50} of Echinacea juice is 50 mL/kg of body weight in mice (Perri *et al.*, 2006).

Equivalent toxic dose in 20 kg dog: 50,000 mg PO of Radix Echinaceae.
Equivalent toxic dose in 5 kg cat: 12,500 mg PO of Radix Echinaceae.

DRUG INTERACTIONS

Validated interactions studies do not exist for Radix Echinaceae preparations. Clinical interactions with other drugs have not been reported. However, because it is an immune stimulant, caution should be used in combining it with immunosuppressive drugs such as corticosteroids, cyclosporine, amiodarone, methotrexate, and ketoconazole (Miller, 1998).

Uncaria tomentosa [Uña de gato] (Cat's Claw)

Uncaria tomentosa is a large, woody vine that derives its name from hook-like thorns that grow along the vine and resemble the claws of a cat. The pentacyclic oxindole alkaloids of Cortex Uncariae Tomentosae affect the cellular immune system (Reinhard, 1999). *In vitro* and *in vivo* studies have demonstrated that the immunostimulating effects of Cortex Uncariae Tomentosae is accomplished by modulating the secretion of multiple cytokines such as interleukin-1, interleukin-6, tumour necrosis factor-alpha, and interferon (Spelman *et al.*, 2011; Lemarie *et al.*, 2000). Two clinical studies have suggested that Cortex Uncariae Tomentosae may be an immunostimulant and increase the number of white blood cells (WHO, 2007).

TOXICOLOGY

Toxicity for Cortex Uncariae Tomentosae has not been documented in dogs and cats when administered orally in therapeutic doses.Oral LD_{50} of freeze-dried aqueous extract of pentacyclic alkaloid-type Radix Uncariae Tomentosae is >16 g/kg of body weight in mice (Reinhard, 1999).

Equivalent toxic dose in 20 kg dog:	>320 g PO of freeze-dried aqueous extract of pentacyclic alkaloid-type Radix Uncariae Tomentosae.
Equivalent toxic dose in 5 kg cat:	>80 g PO of freeze-dried aqueous extract of pentacyclic alkaloid-type Radix Uncariae Tomentosae.

DRUG INTERACTIONS

Validated interactions studies do not exist for Cortex Uncariae Tomentosae preparations. However, Cortex Uncariae Tomentosae inhibits CYP3A4 *in vitro* indicating that it may increase the serum levels of drugs such as non-nucleoside reverse-transcriptase inhibitors, cyclosporine, and some benzodiazepines (Scott & Elmer, 2002). Cortex Uncariae Tomentosae was shown to increase the serum concentrations of atazanavir, ritonavir and saquinavir (López *et al.*, 2008).

Withania somnifera (Ashwagandha)

Radix Withaniae has been known for a spectrum of health-promoting effects including activation of immune, muscle, and neuronal systems (Rajasankar *et al.*, 2009). Radix Withaniae is widely used in modern Western herbalism as an adaptogen. The adaptogenic effect is attributed to the suppression of stress-induced increases of dopamine receptors in the corpus striatum in the brain. Radix Withaniae has shown antioxidant activity in the midbrain and corpus striatum by increasing antioxidant enzyme levels. Stress-induced depletion of T cell population was increased by oral administration of Withanolide A isolated from Radix Withaniae in experimental animals (Kour *et al.*, 2009). It was also found to enhance the immune function by increasing immunoglobulin production and regulating antibody production by augmenting both Th1 and Th2 cytokine production (Yamada *et al.*, 2011).

TOXICOLOGY

Toxicity for Radix Withaniae has not been documented in dogs and cats when administered orally in therapeutic doses. Oral LD_{50} for Radix Withaniae 50% ethanol extract is 1,000 mg/kg of body weight in rats (Williamson, 2002).

Equivalent toxic dose in 20 kg dog: 20, 000 mg PO of Radix Withaniae 50% ethanol extract.
Equivalent toxic dose in 5 kg cat: 5,000 mg PO of Radix Withaniae 50% ethanol extract.

DRUG INTERACTIONS

Validated interactions studies do not exist for Radix Withaniae preparations. Clinical interactions with other drugs have not been reported. However, Radix Withaniae extract may potentiate the sedative effects of barbiturates (Brinker, 2001).

Eleutherococcus senticosus (Eleuthero)

Extracts of Radix Eleutherococci have an adaptogenic effect that produces a non-specific increase in the body's defence against exogenous stress factors and noxious chemicals. The roots also stimulate the immune system, and promote an overall improvement in physical and mental performance (WHO, 2004). Several kinds of chemical compounds have been reported, including triterpenoid saponins, lignans, coumarins, and flavones, among which, phenolic compounds such as syringin and eleutheroside E, were considered to be the most active components. Considerable pharmacological experiments both *in vitro and in vivo* have persuasively demonstrated that Radix Eleutherococci possessed anti-stress, anti-fatigue, immunostimulatory, anti-depressive, antiulcer, anti-inflammatory and hepatoprotective a ctivities (Panossian & Wagner, 2005; Huang *et al.*, 2011).

TOXICOLOGY

Eleutherococcus senticosus

Toxicity for Radix Eleutherococci has not been documented in dogs and cats when administered orally in therapeutic doses. Oral LD_{50} of Radix Eleutherococci is 31 g/kg of body weight in mice (Mills & Bone, 2000).

Equivalent toxic dose in 20 kg dog: 620 g PO of Radix Eleutherococci.
Equivalent toxic dose in 5 kg cat: 155 g PO of Radix Eleutherococci.

DRUG INTERACTIONS

Validated interactions studies do not exist for Radix Eleutherococci preparations. However, Radix Eleutherococci may elevate serum digoxin levels (McRae, 1996). Radix Eleutherococci inhibits metabolism of barbiturates possibly by inhibition of cytochrome P450 2C19. Radix Eleutherococci increases efficacy of the antibiotics monomycin and kanamycin due to enhanced T-lymphocyte activity (Brinker, 2001).

Ligustrum lucidum (Chinese Privet)

Fructus Ligustri Lucidi is a widely used herbal medicine for the treatment of a variety of pathologies (An *et al.*, 2007). Fructus Ligustri Lucidi contains potent immune stimulants which may provide the rational basis for its therapeutic use as a biological response modifier (Sun *et al.*, 1983). Fructus Ligustri Lucidi is found to exert antitumor properties by modulating immune response and by reverting macrophage suppression brought about by tumours (Rittenhouse *et al.*, 1991) and such effects may be due to an increase in phagocytes and lymphokine-activated killer cells (Lau *et al.*, 1994). The secoiridoid glucosides in Fructus Ligustri, have shown strong antioxidant effect against free radical-associated hemolysis of erythrocytes (He *et al.*, 2001). The hepatoprotective effects of Fructus Ligustri Lucidi are due to the oleanolic acid and are thought to be mediated by an increase in hepatic glutathione regeneration capacity (Yim *et al.*, 2001).

TOXICOLOGY

Toxicity for Fructus Ligustri Lucidi has not been documented in dogs and cats when administered orally in therapeutic doses. LD_{50} value for Fructus Ligustri Lucidi has not been determined.

DRUG INTERACTIONS

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

Tinospora sinensis (Chinese Tinospora)

Tinospora sinensis and *Tinospora cordifolia* are two of the indispensable medicinal plants used in veterinary folk medicine and Ayurvedic system of medicine for the treatment of diverse diseases and are recommended for improving the immune system by means of body resistance (Chandrasekaran *et al.*, 2009). In comparative studies of the immunomodulatory activity of *Tinospora cordifolia* and *Tinospora sinensis*, the aqueous extract of *Tinospora sinensis* was found to be more potent (Manjrekar *et al.*, 2000). The chemical constituents reported from Caulis Tinosporae belong to different classes, such as alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoids, phenolics, aliphatic compounds and polysaccharides (Upadhyay *et al.*, 2010). The polysaccharide (1,4)-alpha-D-glucan from Caulis Tinosporae activates the immune system through the activation of macrophages that occurs through Toll-like receptor 6 (TLR6) signalling, NF-kappaB translocation and cytokine production (Nair *et al.*, 2006). Caulis Tinosporae is reported to contain an alpha-glucosidase inhibitor, characterized as saponarin (apigenin-6-C-glucosyl-7-O-glucoside) which has demonstrated hypoglycaemic activity in animal models (Sengupta *et al.*, 2009).

TOXICOLOGY

Toxicity for Caulis Tinosporae has not been documented in dogs and cats when administered orally in therapeutic doses. The LD_{50} value for Caulis Tinosporae has not been determined.

DRUG INTERACTIONS

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

Ocimum sanctum (Holy Basil)

Folium Ocimi Sancti use is described in pharmacopoeias and in traditional systems of medicine for the treatment of arthritis, asthma, bronchitis, common cold, diabetes, fever, influenza, peptic ulcer and rheumatism (WHO, 2004b). Folium Ocimi Sancti has also been suggested to possess anticancer, antidiabetic, antifungal, antimicrobial, hepatoprotective, cardioprotective, antiemetic, antispasmodic, analgesic, adaptogenic and diaphoretic actions. Eugenol (1-hydroxy-2-methoxy-4-allylbenzene), the active constituent present in Folium Ocimi Sancti has been found to be largely responsible for the therapeutic potential of Folium Ocimi Sancti (Prakash & Gupta, 2005). In animal models, oral administration of Folium Ocimi Sancti and Radix Withaniae prevented cadmium-induced peroxidation of tissues (Bharavi *et al.*, 2010) and the combination also exhibited protection against exercise-induced oxidative stress in vital organs (Misra *et al.*, 2009). The anti-stressor activity of Folium Ocimi Sancti is partly attributed to its antioxidant properties (Jyoti *et al.*, 2007). Ocimumoside A isolated from Folium Ocimi Sancti displayed anti-stress effects by normalizing hyperglycemia, plasma corticosterone, plasma creatine kinase, and adrenal hypertrophy in acute stress-induced animal models (Gupta *et al.*, 2007).

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 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 recommended in canine and feline autoimmune diseases.
- 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

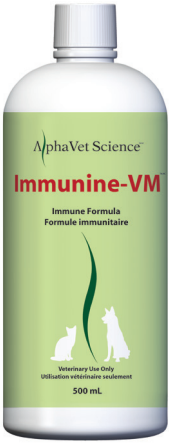
- Mild gastrointestinal discomfort may occur which is dose dependent.

CONTRAINDICATIONS

- Contraindicated in pregnant and nursing dogs and cats.
- Contraindicated in dogs and cats with autoimmune diseases.
- Contraindicated with anticoagulant drugs (dose dependent).

AlphaVet Science™

Immunine-VM™



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