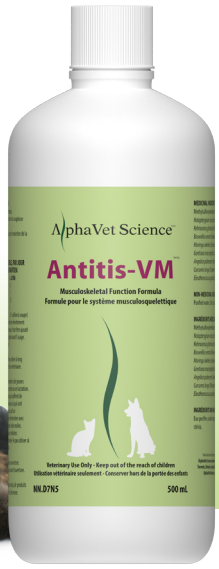
AlphaVet Science™

Antitis-VM™

Musculoskeletal Function Formula NN.D7N5

Antitis-VM™ may help ease aches and discomfort associated with daily activity. This property can be attributed to its antioxidant actions which help remove damaging free radicals thus promoting long-term health.

*ANTITIS is an acronym for **A**ll **N**atural-**T**raditional **I**ngredients **T**o **I**mprove **S**upport



INDICATIONS

- Promotes musculoskeletal health.
- Supports and helps maintain healthy joints and flexibility.
- Provides antioxidant support to maintain health.

INGREDIENTS ACTIONS

- Alterative
- Antioxidant
- Immunomodulator
- Lenitive
- Nutritive

PACKAGING 120 mL/bottle, 500 mL/bottle

ADMINISTRATION Syringe directly into the mouth for best results. Can be added to animal's food. Shake well before use. For use in cats & dogs only.

DIRECTIONS

ADMINISTER ORALLY PER DAY			
LBS	**ONCE**	**DOSAGE**	
		mL	**Teaspoon(s)**
1-10	0.5-4.5	2.5	0.5
10.1-20	4.6-9	5	1
20.1-50	9.1-22.6	7.5	1.5
50.1-100	22.7-45.4	10	2
>100	45.4	15	3 (1 Tablespoon)

STORAGE Refrigerate after opening. Consume within six (6) months after opening. Keep bottle cap tightly closed when not in use.

Antitis-VM™ FORMULA

MEDICINAL INGREDIENTS PER 1 TEASPOON (5 mL)

Methylsulfonylmethane (MSM) ..... 250 mg

Notopterygium incisum, Syn. *Hansenia weberbaueriana*
(Notopterygium Root/ Rhizoma et Radix Notopterygii) ..... 250 mg

Rehmannia glutinosa (Rehmannia Root/Radix Rehmanniae Glutinosae) ..... 125 mg

Boswellia serrata (Frankincense Resin/Gummi Boswellii) ..... 100 mg

Moringa oleifera (Drumstick Tree Seed/Semen Moringae) ..... 100 mg

Gentiana macrophylla (Largeleaf Gentian Root/Radix Gentianae Macrophyllae) ..... 75 mg

Angelica pubescens (Angelica Root/Radix Angelicae Pubescentis) ..... 50 mg

Curcuma longa (Turmeric Rhizome/Rhizoma Curcumae Longae) ..... 50 mg

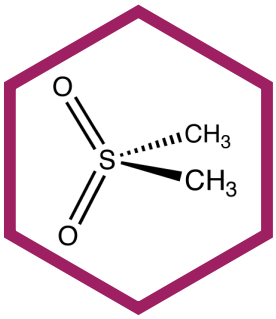
Eleutherococcus gracilistylus, Syn. *Acanthopanax gracilistylus*
(Acanthopanax Bark/Cortex Acanthopanacis) ..... 50 mg

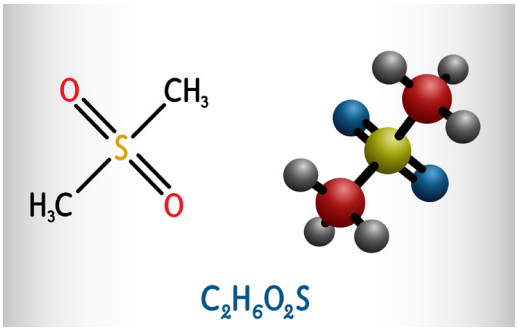
NON-MEDICINAL INGREDIENTS

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

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

Methylsulfonylmethane (MSM) [$C_2H_6O_2S$]





Methylsulfonylmethane (MSM), naturally occurring in green plants, fruits and vegetables, has been shown to exert anti-inflammatory and antioxidant effects (Amirshahrokhi et al., 2011). MSM inhibits the release of nitric oxide and prostaglandin E2 by alleviating the expression of inducible nitric oxide synthase and cyclooxygenase-2 (Kim et al., 2009). In the ulcerative colitis animal model, MSM demonstrates a protective effect by reducing the colonic levels of malondialdehyde, myeloperoxidase, and interleukin-1 beta (Amirshahrokhi et al., 2011). In a prospective randomized clinical trial of human gonarthrosis, a combination of MSM and boswellic acids from Gummi Boswellii demonstrated an anti-inflammatory effect and the need for anti-inflammatory drugs (Notamicola et al., 2011). In two other human clinical trials, treatment with MSM showed significant improvement in pain in osteoarthritis (Brien et al., 2008).

TOXICOLOGY

Toxicity for MSM has not been documented in dogs and cats when administered orally in therapeutic doses. In rats, no adverse effects with MSM after a 2 g/kg daily dose. In a 90-day follow-up study, rats received daily MSM doses of 1.5 g/kg and no changes in symptoms, blood chemistry or gross pathology (Horváth et al., 2002).

DRUG INTERACTIONS

Validated interaction studies do not exist for MSM. Clinical interactions with other drugs have not been reported.

Notopterygium incisum (Syn. *Hansenia weberbaueriana*) [Notopterygium] (Root)

Rhizoma et Radix Notopterygii consists of the dried rhizomes and roots of *Hansenia weberbaueriana* (Fedde ex H.Wolff) Pimenov & Kljuykov. (Apiaceae). In experimental studies, the active constituents of Rhizoma et Radix Notopterygii phenethyl ferulate and falcarindiol reduce inflammation by inhibiting the activity of 5-lipoxygenase and cyclooxygenase (Zschocke et al., 1997). Notopterol, a chemical constituent of Rhizoma et Radix Notopterygii, exhibits analgesic properties. Notopterol is also known as an anti-inflammatory agent by its inhibitory effect on vascular permeability (Okuyama et al., 1993). In a human 24-week randomized controlled trial, an herbal formula containing Rhizoma et Radix Notopterygii improved morning stiffness, grip strength and joint tenderness in rheumatoid arthritis patients (Chen et al., 2010).

TOXICOLOGY

Toxicity for Rhizoma et Radix Notopterygii has not been documented in dogs and cats when administered orally in therapeutic doses.

No fatalities were observed in mice following oral ingestion of aqueous extract of Radix Notopterygii at 12 g/kg. Oral LD50 for essential oil of Rhizoma et Radix Notopterygii is 2.83 g/kg (Chen & Chen, 2004).

The equivalent toxic dose in a 20 kg dog: 56.6 g PO of Rhizoma et Radix Notopterygii essential oil.

The equivalent toxic dose in a 5 kg cat: 14.15 g PO of Rhizoma et Radix Notopterygii essential oil.

DRUG INTERACTIONS

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

Rehmannia glutinosa (Rehmannia) [Root]

Radix Rehmanniae Glutinosae consists of the processed roots of *Rehmannia glutinosa* (Gaertn.) Libosch. ex Steud. (Scrophulariaceae). It is a traditional Chinese medicine with anti-inflammatory properties (Sung et al., 2011). Radix Rehmanniae Glutinosae contains more than 70 compounds such as iridoids, saccharides, amino acids, inorganic ions, and other trace elements. Studies show that Radix Rehmanniae Glutinosae and its active principles possess broad pharmacological actions on the immune, endocrine, cardiovascular, and nervous systems (Zhang et al., 2008). Radix Rehmanniae Glutinosae has shown potent scavenging activity against superoxide radicals, hydroxyl radicals, hydrogen peroxide, and 2,2- diphenyl-1-picrylhydrazyl (DPPH) radical (Yu et al., 2006a). It also increases the activity of antioxidant enzymes and the level of glutathione (Yu et al., 2006b).

TOXICOLOGY

Toxicity for Radix Rehmanniae Glutinosae has not been documented in dogs and cats when administered orally in therapeutic doses.

Oral LD50 for 70% methanol extract of Radix Rehmanniae Glutinosae is >2.0 g/kg in mice (WHO, 2007).

The equivalent toxic dose in a 20 kg dog: >40 g PO of 70% methanol extract of Radix Rehmanniae Glutinosae.

The equivalent toxic dose in a 5 kg cat: >10 g PO of 70% methanol extract of Radix Rehmanniae Glutinosae.

DRUG INTERACTIONS

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

However, caution should be taken when used with drugs metabolized by CYP3A4 as Radix Rehmanniae Glutinosae could activate pregnane X receptor (PXR) signalling pathway and induce CYP3A4 reporter gene (Yu et al., 2011).

Boswellia serrata (Frankincense) [Resin]

Gummi Boswellii consists of the dried gum resin of *Boswellia serrata* Roxb. ex Colebr. (Burseraceae) [WHO, 2009]. Boswellic acids, the principal constituent of Gummi Boswellii, contribute to most of the herb's pharmacological activities. Animal studies and clinical trials support the potential of Gummi Boswellii for the treatment of inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, and bronchial asthma. In inflammatory response, the molecular targets of Gummi Boswellii are inhibition of microsomal prostaglandin E synthase-1, serine protease cathepsin G, and suppression of leukotriene formation via inhibition of 5-lipoxygenase. These actions are due to boswellic acids such as β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid (Safayi et al., 1997; Siemoneit et al., 2009; Kunnumakkara et al., 2009; WHO, 2009; Abdel-Tawab et al., 2011).

Canine studies of Gummi Boswellii and combinations

Studies-Canine	Study Title	Study Summary
Reichling et al., 2004	Dietary support with Boswellia resin in canine inflammatory joint and spinal disease.	In the open multi-centre veterinary clinical trial in dogs with osteoarthritis and degenerative conditions, dietary support with Gummi Boswellii demonstrated a statistically significant reduction of severity and resolution of clinical signs such as intermittent lameness, local pain and stiff gait.
Caterino et al., 2021	Clinical efficacy of Curcuvet and Boswellic acid combined with conventional nutraceutical product: An aid to canine osteoarthritis.	In the randomized, double-blind trial of 20 osteoarthritis canine subjects, administration of boswellic acid and curcumin reduced lameness and pain.
Bampidis et al., 2022	Scientific Opinion on the safety and efficacy of a feed additive consisting of an extract of olibanum from Boswellia serrata Roxb. ex Colebr. for use in dogs and horses (FEFANA asbl).	For the use of Gummi Boswellii in dogs, the European Food Safety Authority Panel on Additives and Products or Substances used in Animal Feed calculated the safe concentration of extracts containing ≥65% of boswellic acids is 330 mg/kg of complete feed.

Martello et al., 2022	Efficacy of a dietary supplement in dogs with osteoarthritis: A randomized placebo-controlled, double-blind clinical trial.	The study results support the use of dietary supplement formula containing Gummi Boswellii extract as a potentially effective treatment in cases with different clinical conditions, levels of chronic pain and joint involvement. The tested product was beneficial in alleviating pain and reducing clinical signs in dogs with osteoarthritis. There were no adverse effects for the product tested.

TOXICOLOGY

Toxicity for Gummi Boswellii has not been documented in dogs and cats when administered orally in therapeutic doses.

In toxicity studies of Gummi Boswellii extract in rats and mice, the oral and intraperitoneal LD50 has been established at >2 g/kg (Singh & Atal, 1986).

The equivalent toxic dose in a 20 kg dog: >40 g PO and IP of Gummi Boswellii extract.
The equivalent toxic dose in a 5 kg cat: >10 g PO and IP of Gummi Boswellii extract.

DRUG INTERACTIONS

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

Moringa oleifera (Drumstick Tree) [Seed]

Moringa oleifera Lam. (Moringaceae) has an impressive range of medicinal uses with high nutritional value. Different parts of this plant contain a profile of crucial minerals and are a good source of protein, vitamins, beta-carotene, amino acids and various phenolics. Folium cum Semen

Moringae provides a unique combination of zeatin, quercetin, beta-sitosterol, caffeoylquinic acid and kaempferol. The leaves, roots, seed, bark, fruit, flowers and immature pods of *Moringa oleifera* act as cardiac and circulatory stimulants. It also possesses antitumor, antipyretic, antiepileptic, anti-inflammatory, antiulcer, antispasmodic, diuretic, antihypertensive, cholesterol-lowering, antioxidant, antidiabetic, hepatoprotective, antibacterial and antifungal activities (Anwar et al., 2007).

In arthritic animal models, Semen Moringae has demonstrated anti-inflammatory properties by altering oxidative stress (Mahajan et al., 2007) and inhibiting the production of inflammatory mediators such as interleukine-6, tumor necrosis factor-alpha, inducible nitric oxide synthase, and cyclooxygenase-2 (Muangnoi et al., 2012).

Canine studies of *Moringa oleifera* and combinations

Studies-Canine	Study Title	Study Summary
Abakpa et al., 2017	Haematological and Biochemical Changes in Alloxan-Induced Diabetic Dogs Treated with Aqueous Extract of Moringa oleifera Leaves.	*Moringa oleifera* has a hypoglycaemic effect and can be beneficial in the clinical management of diabetes mellitus in dogs.

TOXICOLOGY

In acute toxicity studies in rats, Folium Moringae aqueous extracts showed no toxicity or mortality at a 2,000 mg/kg oral dose (Adedapo et al., 2009). The LD50 for the hydro-ethanol extract of Semen Moringae in mice is 1,800 mg/kg administered through gastric intubation (Paliwal et al., 2011).

The equivalent toxic dose in a 20 kg dog: 36,000 mg of Semen Moringae hydro-ethanol extract via gastric intubation.

The equivalent toxic dose in a 5 kg cat: 9,000 mg of Semen Moringae hydro-ethanol extract via gastric intubation.

DRUG INTERACTIONS

In a pre-clinical study, isolated fractions of Semen Moringae inhibited cytochrome P-450 and increased the bioavailability of rifampicin (Pal et al., 2011)

Gentiana macrophylla (Large-leaf Gentian) [Root]

Radix Gentianae Macrophyllae consists of the dried root of *Gentiana macrophylla* Pall. (Gentianaceae). Extracts of Radix Gentianae Macrophyllae exhibit potent anti-inflammatory action. In the rheumatic animal model, oral administration of Radix Gentianae Macrophyllae extract reduced prostaglandin E2 levels in the inflammatory tissues, and anti-inflammatory activity was comparable to that observed in prednisone (Yu et al., 2004). Gentianine, a chemical constituent of Radix Gentianae Macrophyllae, has also demonstrated anti-inflammatory action by suppressing the production of pro-inflammatory cytokines such as TNF-alpha and IL-6 (Kwak et al., 2005).

TOXICOLOGY

Toxicity for Radix Gentianae Macrophyllae has not been documented in dogs and cats when administered orally in therapeutic doses.

Oral LD50 for gentianine, an active constituent of Radix Gentianae Macrophyllae, is 480 mg/kg in mice (Chen & Chen, 2004).

The equivalent toxic dose in a 20 kg dog: 9,600 mg PO of gentianine, an active constituent of Radix Gentianae Macrophyllae.

The equivalent toxic dose in a 5 kg cat: 2,400 mg PO of gentianine, an active constituent of Radix Gentianae Macrophyllae.

DRUG INTERACTIONS

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

Angelica pubescens (Pubescent Angelica) [Root]

Radix Angelicae Pubescentis is the dried root of *Angelica pubescens* Maxim (Apiaceae), a traditional Chinese medicinal herb used to treat arthritis. In animal models, the active chemical compounds of Angelicae Pubescentis, such as columbianadin, columbianetin acetate, bergapten, umbelliferone, and caffeic acid, significantly demonstrated anti-inflammatory and analgesic activities. Other active constituents such as osthol and xanthotoxin have exhibited anti-inflammatory activity and isoimperatorin an analgesic effect (Chen et al., 1995). The active constituent osthol inhibits inflammatory mediators such as 5-lipoxygenase and cyclooxygenase (Liu et al., 1998).

TOXICOLOGY

Toxicity for Radix Angelicae Pubescentis has not been documented in dogs and cats when administered orally in therapeutic doses.

In rats, the intramuscular LD50 for xanthotoxin and bergapten is 160 mg/kg and 945 mg/kg, respectively (Chen & Chen, 2004).

The equivalent toxic dose in a 20 kg dog: 3,200 mg IM of xanthotoxin and 18,900 mg of bergapten.

The equivalent toxic dose in a 5 kg cat: 800 mg IM of xanthotoxin and 4,725 mg of bergapten.

DRUG INTERACTIONS

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

However, osthole, an active constituent of Radix Angelicae Pubescentis, may increase the effects of sodium nitroprusside (Nitropress) *in vitro* (Teng et al., 1994).

Curcuma longa (Turmeric) [Rhizome]

Rhizoma Curcumae Longae consists of the dried rhizome of *Curcuma longa L.* (Zingiberaceae). Pharmacopeias and traditional systems of medicine describe the use of Rhizoma Curcumae Longae in conditions associated with pain and inflammation, such as osteoarthritis, rheumatoid arthritis, peptic ulcers, dysmenorrhoea, asthma, and hepatitis (WHO, 1999). Curcumin and its derivatives are the active anti-inflammatory constituents of Rhizoma Curcumae Longae (Masuda et al., 1993). The anti-inflammatory activity of curcumin may be due to its ability to scavenge oxygen radicals (Kunchandy & Rao, 1990) and in the regulation of inflammatory cytokines such as tumour necrosis factor, interleukin-1 and interleukin-6 (Zhou et al., 2011).

Canine and feline studies of Rhizoma Curcumae Longae and combinations

Studies-Canine	Study Title	Study Summary
Leray et al., 2011	Effect of citrus polyphenol- and curcumin-supplemented diet on inflammatory state in obese cats.	Administration of curcumin to obese cats improved the obesity-related inflammatory state.
Colitti et al., 2012	Transcriptome modification of white blood cells after dietary administration of curcumin and non-steroidal anti-inflammatory drug in osteoarthritic affected dogs.	The study suggested that curcumin offers complimentary anti-inflammatory support for osteoarthritis treatment in dogs.
Comblain et al., 2017	A randomized, double-blind, prospective, placebo-controlled study of the efficacy of a diet supplemented with curcuminoids extract, hydrolyzed collagen and green tea extract in owner's dogs with osteoarthritis.	In a randomly allocated, double-blind, prospective, placebo-controlled study on dogs with naturally occurring osteoarthritis, administration of a mixture containing Rhizoma Curcumae Longae extract for three months reduced pain.

Campigotto et al., 2020	Dog food production using curcumin as antioxidant: effects of intake on animal growth, health and feed conservation.	Administration of curcumin to dogs increased the activity of several antioxidant enzymes in addition to non-protein thiols and the total antioxidant capacity in the serum, consequently reducing levels of reactive oxygen species. The study concluded that curcumin improved animal health via stimulation of the antioxidant system and evidence of an anti-inflammatory effect.
Deng et al., 2020	Chemically-Modified Curcumin 2.24: A Novel Systemic Therapy for Natural Periodontitis in Dogs.	In a dog model of natural periodontitis, oral administration of chemically-modified curcumin significantly decreased clinical measures of periodontitis as well as pro-inflammatory cytokines, matrix metalloproteinases, and cell-signalling molecules.
Caterino et al., 2021	Clinical efficacy of Curcuvet and Boswellic acid combined with conventional nutraceutical product: An aid to canine osteoarthritis.	In the randomized, double-blind trial of 20 osteoarthritis canine subjects, administration of boswellic acid and curcumin reduced lameness and pain.

TOXICOLOGY

Toxicity for Rhizoma Curcumae Longae has not been documented in dogs and cats when administered orally in therapeutic doses. Feeding pups with Rhizoma Curcumae Longae 500 mg/kg for three months was safe with no toxicity (WHO, 1980).

Oral LD50 of Rhizoma Curcumae Longae is >1,000 mg/kg in rats (Pandey, 2011).

Equivalent toxic dose in a 20 kg dog: >20,000 mg PO of Rhizoma Curcumae Longae.

Equivalent toxic dose in a 5 kg cat: >5,000 mg PO of Rhizoma Curcumae Longae.

DRUG INTERACTIONS

In animal studies, pre-treatment with curcumin, a major active component of Rhizoma Curcumae Longae, resulted in increased plasma elimination half-life of the broad-spectrum antibacterial agent norfloxacin, hence reducing the dosage of the drug (Pavithra et al., 2009).

Curcumin can downregulate the intestinal P-Glycoprotein levels. It can increase the concentration of Celiprolol (beta-blocker) and midazolam (benzodiazepine) in rats (Zhang et al., 2007).

Curcumin may enhance the effect and decrease the toxicity of the antifungal drug amphotericin B *in vitro* (Kudva et al., 2011).

Curcumin can enhance the effects of chemotherapeutic agents such as mitomycin C (Ko et al., 2011) and cisplatin (Tsai et al., 2011) *in vitro.*

Rhizoma Curcumae Longae inhibits camptothecin, mechlorethamine, and doxorubicin-induced apoptosis of breast cancer cell lines *in vitro* (Somasundaram et al., 2002).

Rhizoma Curcumae Longae may increase the risk of bleeding when taken with anticoagulants/antiplatelet drugs (Brinker, 1998).

Eleutherococcus gracilistylus (Syn. *Acanthopanax gracilistylus*) [Acanthopanax] (Bark)

Cortex Acanthopanacis consists of the dried root bark of *Acanthopanax gracilistylus* W. W. Smith. (Araliaceae) [PPRC, 2005]. It is an ingredient in different traditional medicine recipes in China (Wu Jia Pi), Japan (Gokahi), and Korea (Ogapi) [Kim et al., 2014].

Cortex Acanthopanacis possesses potent anti-inflammatory and antioxidant activities. Chemical constituents such as triterpenoids, monoterpenoids, and diterpenoids have been isolated from Cortex Acanthopanacis, of which diterpenoids are closely related to their pharmacological properties. The anti-inflammatory mechanism of action includes the inhibition of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-8, and tumor necrosis factor (TNF)-α (Wu et al., 2014). The anti-oxidative capability of Cortex Acanthopanacis results from the presence of protocatechuic and trans-caffeic acids (Załuski et al., 2017).

TOXICOLOGY

Toxicity for Cortex Acanthopanacis has not been documented in dogs and cats when administered orally in therapeutic doses.

LD50 for Cortex Acanthopanacis has not been determined.

DRUG INTERACTIONS

Cortex Acanthopanacis has an inhibitory effect on the central nervous system to induce sedation. It potentiates the sedative effects of barbiturates (Chen & Chen, 2004).

PRECAUTIONS

- Do not use in immature, pregnant or lactating animals.
- Do not use in animals with diabetes, gastrointestinal ulceration or receiving other drugs, unless directed by a veterinarian.
- Use with caution in animals with loose stools.
- May cause drowsiness or sedation.
- Not to be used one week before 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 the incidence of gastrointestinal upset.
- Do not exceed recommended dose.
- Shake well before use
- Do not use if security seal is broken.

WARNINGS

- To be used in dogs and cats only.
- Keep out of the 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.

DURATION OF USE

- Not for long term use, unless directed by a veterinarian.

AlphaVet Science™

Antitis-VM™

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