AlphaVet Science

Articulare-VM™

Articulation Formula **NN.0651**

Articulare-VM™ helps maintain the structural integrity of joints and connective tissues, thus improving joint mobility and flexibility

INDICATIONS
- Promotes articulation health.
- Helps maintain joint health.
- Helps maintain structural integrity of joints and connective tissues.

INGREDIENTS ACTIONS
- Alterative
- Antioxidant
- Nutritive
- Lenitive

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 ONCE PER DAY			
LBS	**KG**	**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.

Articulare-VM™ FORMULA

MEDICINAL INGREDIENTS PER 1 TEASPOON (5 mL):

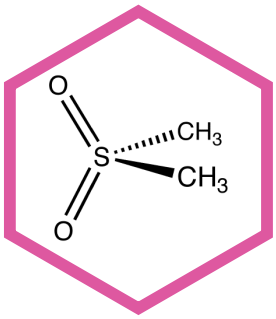
Methylsulfonylmethane (MSM)	500 mg
D-Glucosamine sulphate (Shellfish Exoskeletons)	300 mg
Glucosamine hydrochloride (Shellfish Exoskeletons)	175 mg
Chondroitin sulphate (Bovine Cartilage)	150 mg
N-Acetylglucosamine (NAG)	25 mg
Boswellia serrata (Frankincense Resin/Gummi Boswellii)	20 mg
Curcuma longa (Turmeric Rhizome/Rhizoma Curcumae Longae)	20 mg
Harpagophytum procumbens (Devil's Claw Root/Radix Harpagophyti)	20 mg
Moringa oleifera (Drumstick Tree Seed/Semen Moringae)	20 mg
Saposhnikovia divaricata, Syn. *Ledebouriella divaricata* (Siler Root/Radix Saposhnikoviae)	10 mg

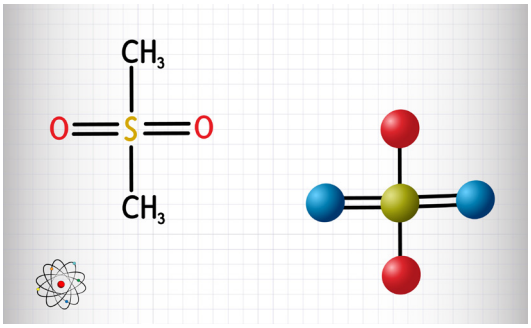
NON-MEDICINAL INGREDIENTS

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

Articulare-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) [$C_2H_6O_2S$]





MSM, also known as dimethyl sulfone and methyl sulfone, is an organosulfur compound occurring naturally in fruits, vegetables, grains, and animals, including humans. As a therapeutic agent, MSM utilizes its unique penetrability properties to alter physiological effects at the cellular and tissue levels. Furthermore, MSM can act as a carrier or co-transporter for other therapeutic agents, even furthering its potential applications (Butawan et al., 2017).

Clinical evidence for the usefulness of MSM consists of published studies on both animals and humans, and these studies have suggested some benefits in the treatment of osteoarthritis. After several reports that MSM helped arthritis in animal models, a double-blind, placebo-controlled human study found that 500 mg TID of MSM (alone or in combination with glucosamine sulphate 500 mg) helped relieve symptoms of knee osteoarthritis (Usha & Naidu, 2004). In another study of human osteoarthritis, MSM (3g twice a day) improved symptoms of pain and physical function without major adverse events (Kim et al., 2006). Similar results were also seen in patients with osteoarthritis receiving MSM in doses of 1.125 grams, three times daily for 12 weeks (Debbi et al., 2011).

TOXICOLOGY

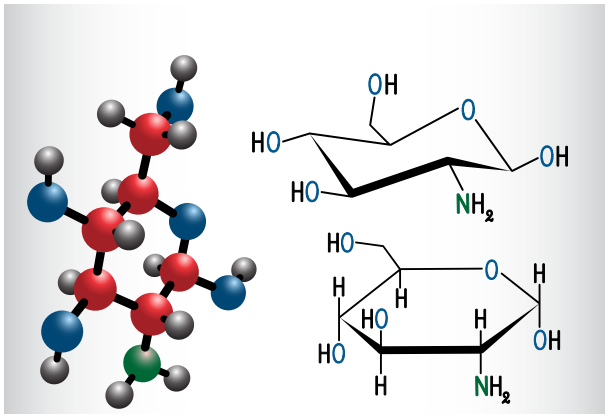
Toxicity for MSM has not been documented in dogs and cats when administered orally in therapeutic doses. In several toxicity studies on rats, mice, and dogs, MSM is well-tolerated and safe (Butawan et al., 2017).

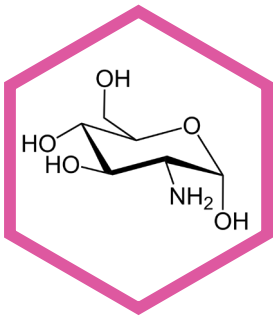
In rats, no adverse effects were reported with MSM after a 2 g/kg daily dose. In the 90-day follow-up study, rats receiving daily MSM doses of 1.5 g/kg had no changes in blood chemistry or gross pathology (Horváth et al., 2002).

DRUG INTERACTIONS

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

D-Glucosamine sulphate ($C_6H_{15}NO_9S$) and Glucosamine hydrochloride ($C_6H_{14}ClNO_5$)





"In dogs, glucosamine in liquid form provides higher plasma concentration than the chewable or tablet formulations." (Maxwell et al., 2016).

Glucosamine (2-amino-2-deoxy-β-d-glucopyranose) is an endogenous amino monosaccharide synthesized from glucose and utilized for the biosynthesis of glycoproteins and glycosaminoglycans. The rationale for using glucosamine in osteoarthritis stems from the metabolic pathway of glycosaminoglycan production. Supplemental glucosamine is available as sulfate, hydrochloride, N-acetyl-glucosamine, and dextrorotatory isomer (Dahmer et al., 2008).

Cartilage is associated with a complex extracellular matrix composed of glycosaminoglycans and proteoglycans, which interact with collagen and elastic fibres. The glycosaminoglycans in the connective tissue include keratan sulfate, dermatan sulfate, heparan sulfate, chondroitin sulfate, and hyaluronic acid. D-Glucosamine is the hexosamine component of keratan sulfate and hyaluronic acid (Barclay & Tsourounis, 1998).

In short-term clinical trials, glucosamine provided effective symptomatic relief for patients with osteoarthritis. In addition, glucosamine has shown promising results in modifying the progression of arthritis over three years (Matheson & Perry, 2003). A systematic review of clinical trials of various treatments for osteoarthritis in dogs using the FDA's evidence-based medicine scoring system found a moderate level of comfort in using a combination of glucosamine hydrochloride and chondroitin sulphate (Aragon et al., 2007).

Canine and feline Studies of Glucosamine sulphate/ Glucosamine hydrochloride and combinations

Studies-Canine	Study Title	Study Summary
Johnson et al., 2001	Effects of an orally administered mixture of chondroitin sulfate, glucosamine hydrochloride and manganese ascorbate on synovial fluid chondroitin sulfate 3B3 and 7D4 epitope in a canine cruciate ligament transection model of osteoarthritis.	In a canine model of surgically induced osteoarthritis, oral administration of a mixture containing chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate resulted in the modulation of articular cartilage metabolism.
Adebowale et al., 2002	The bioavailability and pharmacokinetics of glucosamine hydrochloride and low molecular weight chondroitin sulfate after single and multiple doses to beagle dogs.	The study demonstrates that glucosamine hydrochloride and chondroitin sulfate are bioavailable after oral dosing.
D'Altilio et al., 2007	Therapeutic Efficacy and Safety of Undenatured Type II Collagen Singly or in Combination with Glucosamine and Chondroitin in Arthritic Dogs.	Data of this placebo-controlled study demonstrate that daily treatment of arthritic dogs with collagen or in combination with glucosamine and chondroitin markedly alleviates arthritic-associated pain, and these supplements are well-tolerated with no side effects noted.
McCarthy et al., 2007	Randomised double-blind, positive-controlled trial to assess the efficacy of glucosamine/chondroitin sulfate for the treatment of dogs with osteoarthritis.	In the randomized, double-blind, positive controlled, multi-centre trial of dogs with osteoarthritis, orally-administered glucosamine hydrochloride and chondroitin sulfate showed a positive clinical effect.
Minami et al., 2011	Clinical application of d-glucosamine and scale collagen peptide on canine and feline orthopedic diseases and spondylitis deformans.	The simultaneous administration of D-glucosamine and fish scale collagen was beneficial in various kinds of joint degeneration and spondylitis deformans in dogs and cats.
Gupta et al., 2012	Comparative therapeutic efficacy and safety of type-II collagen (UC-II), glucosamine and chondroitin in arthritic dogs: pain evaluation by ground force plate.	Moderately arthritic dogs treated with type-II collagen alone or in combination with glucosamine hydrochloride and chondroitin sulphate showed a marked reduction in arthritic pain with maximum improvement and well-tolerated.
Osaki et al., 2012	Metabolomic analyses of blood plasma after oral administration of D-glucosamine hydrochloride to dogs.	Oral administration of D-glucosamine hydrochloride in dogs promotes cartilage regeneration.

Maxwell et al., 2016	Comparison of Glucosamine Absorption After Administration of Oral Liquid, Chewable, and Tablet Formulations to Dogs.	The study demonstrated maximum plasma glucosamine concentration was higher for the liquid supplement.
Martello et al., 2022	Efficacy of a dietary supplement in dogs with osteoarthritis: A randomized placebo-controlled, double-blind clinical trial.	In the randomized, placebo-controlled, double-blinded trial of dogs with osteoarthritis, an orally-administered mixture of Boswellia, chlorophyll, green tea extract, glucosamine, chondroitin sulfate, hyaluronic acid, and collagen proved to be significantly beneficial in alleviating pain and in reducing the clinical signs of osteoarthritis.

TOXICOLOGY

Toxicity for glucosamine sulphate and glucosamine hydrochloride has not been documented in dogs and cats when administered orally in therapeutic doses.

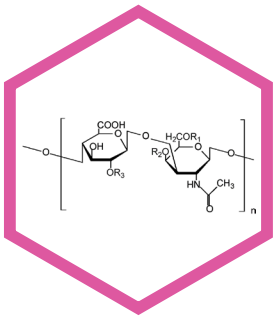
The LD50 of glucosamine sulphate and glucosamine hydrochloride has not been determined. No mortality in mice and rats was observed with glucosamine sulfate at a dose of 5,000 mg/kg PO, 3,000 mg/kg IM, and 1500 mg/kg IV (Senin et al., 1987).

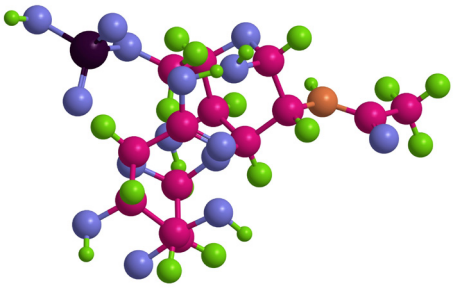
DRUG INTERACTIONS

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

However, in a case report, a potential interaction exists between the anticoagulant drug warfarin and glucosamine-chondroitin that is associated with an increase in the international normalized ratio (INR) (Knudsen & Sokol, 2008).

Chondroitin sulphate ($C_{13}H_{21}NO_{15}S$)





Chondroitin sulphate is a sulphated glycosaminoglycan which is a crucial component of the extracellular matrix of many connective tissues, including cartilage, bone, skin, ligaments and tendons. In the cartilage, it provides much of its resistance to compression (Baeurle et al., 2009). Studies investigating chondroitin sulphate's specific actions have found that it inhibits the production of stromelysin, an enzyme that degrades cartilage tissue (Monfort et al., 2005). Osteoarthritis Research Society International (OARSI) recommends chondroitin sulphate as the second most effective treatment for moderate cases of osteoarthritis (Zhang & Moskowitz, 2007).

Chondroitin sulphate is mainly obtained from bovine, porcine or marine cartilage and has a molecular weight of 50-100kDa that lowers to 10-40kDa after extraction. It is readily absorbed in the gastrointestinal tract and reaches the blood compartment as 10% chondroitin sulfate and 90% depolymerized low-molecular-weight derivatives (Henrotin et al., 2010).

Canine and feline studies of Chondroitin sulphate and combinations

Studies-Canine	Study Title	Study Summary
Adebowale et al., 2002	The bioavailability and pharmacokinetics of glucosamine hydrochloride and low molecular weight chondroitin sulfate after single and multiple doses to beagle dogs.	The low molecular weight chondroitin sulfate used in this study displays significant accumulation upon multiple dosing.
Dobenecker et al., 2002	A placebo-controlled double-blind study on the effect of nutraceuticals (chondroitin sulfate and mussel extract) in dogs with joint diseases as perceived by their owners.	In the placebo-controlled double-blind study of dogs with joint diseases, administration of chondroitin sulfate or mussel extract showed some improvement.
Chang et al., 2007	Osteochondrodysplasia in three Scottish Fold cats.	In feline subjects with Scottish fold disease, oral glucosamine and chondroitin sulfate reduced pain without adverse effects.

Gonçalves et al., 2008	Effects of chondroitin sulfate and sodium hyaluronate on chondrocytes and extracellular matrix of articular cartilage in dogs with degenerative joint disease.	In canine subjects with experimentally induced degenerative joint disease, oral administration of chondroitin sulfate stimulated the chondrocyte metabolic activity and decreased the degenerative process.
Lascelles et al., 2010	Evaluation of a therapeutic diet for feline degenerative joint disease.	In the randomized, controlled, blinded, parallel-group, prospective clinical study of cats with degenerative joint disease, a diet high in EPA and DHA and supplemented with green-lipped mussel extract and glucosamine/chondroitin sulfate improved objective measures of mobility.

TOXICOLOGY

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

The LD50 for chondroitin sulphate, sodium salt in rats: oral >10,000 mg/kg; intraperitoneal 2,900 mg/kg; subcutaneous 3,700 mg/kg; intravenous >3,125 mg/kg. The LD50 for chondroitin sulphate, sodium salt in mice: oral >10,000 mg/kg; intraperitoneal 9,800 mg/kg; subcutaneous >10,000 mg/kg; intravenous 4,980 mg/kg (TRI, 2002).

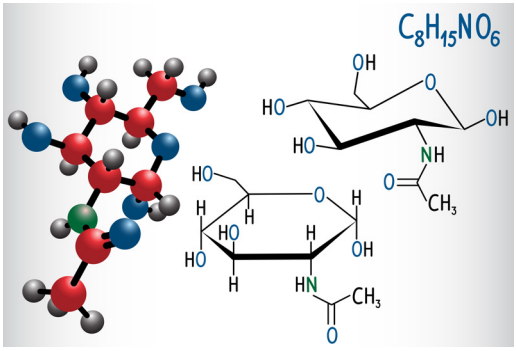
The equivalent toxic dose in a 20 kg dog: >200,000 mg PO of chondroitin sulphate.
The equivalent toxic dose in a 5 kg cat: >50,000 mg PO of chondroitin sulphate.

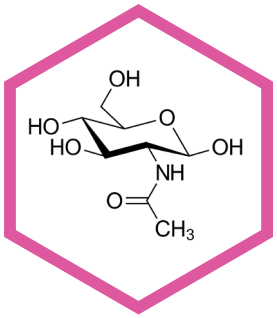
DRUG INTERACTIONS

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

Note: Chondroitin sulphate is not metabolized by cytochrome P450. This is in favour of a very low risk of interaction with other drugs (Henrotin et al., 2010).

N-Acetylglucosamine ($C_8H_{15}NO_6$)





N-acetylglucosamine (NAG or GlcNAc) is a monosaccharide and the monomeric unit of the polymer chitin, the second most abundant carbohydrate after cellulose. It is also a fundamental component of hyaluronic acid and keratin sulfate, which act as a cushion in joints to absorb mechanical shock. Preparations containing NAG are by oral, transmucosal, parenteral, and topical administration and the results from these deliveries indicate that NAG significantly enhances the prevention of joint damage (Chen et al., 2010). Oral administration of NAG at doses of 500 and 1,000 mg/day improves cartilage metabolism in healthy human subjects without apparent adverse effects (Kubomura et al., 2017).

Canine studies of *N*-Acetylglucosamine and combinations

Studies-Canine	Study Title	Study Summary
Osaki et al., 2015	Metabolomic Analysis of Blood Plasma after Oral Administration of N-acetyl-d-Glucosamine in Dogs.	Oral administration of NAG in dogs increased ectoine levels in the plasma. Increased ectoine concentration may be important for protecting the skin from the effects of UVA-induced cell damage and maintaining skin moisture.

TOXICOLOGY

Toxicity for *N*-acetylglucosamine has not been documented in dogs and cats when administered orally in therapeutic doses.

Toxicity tests reveal that *N*-acetylglucosamine is non-toxic, supporting the essential safety issue (Chen et al., 2010).

DRUG INTERACTIONS

Validated interactions studies do not exist for *N*-acetylglucosamine preparations. Clinical interactions with other drugs have not been reported.

Boswellia serrata (Frankincense) [Resin]

Boswellia serrata (Salai or Salai guggul) is a moderate to large-sized branching tree of the family Burseraceae (Genus Boswellia), which grows in dry mountainous regions of India, Northern Africa and the Middle East (Siddiqui, 2011). Gummi Boswellii consists of the dried gum resin of *Boswellia serrata* Roxb. ex Colebr [WHO, 2009]. The oleo gum resins contain 30-60% resin and 5-10% essential oils, which are soluble in organic solvents, and the rest is polysaccharides (Siddiqui, 2011).

Gummi Boswellii possesses monoterpenes, diterpenes, triterpenes, tetracyclic triterpenic acids and four pentacyclic triterpenic acids. They include β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, which are responsible for the inhibition of pro-inflammatory enzymes. Of these four boswellic acids, acetyl-11-keto-β-boswellic acid is the most potent inhibitor of 5-lipoxygenase, an enzyme responsible for inflammation (Siddiqui, 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.	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 interaction studies do not exist for Gummi Boswellii preparations. Clinical interactions with other drugs have not been reported.

Curcuma longa (Turmeric) [Rhizome]

Rhizoma Curcumae Longae is the dried rhizome of *Curcuma longa* L. (Zingiberaceae), and curcumin is the principal curcuminoid (WHO, 1999). Traditionally, it is used in Herbal Medicine as an anti-inflammatory to help relieve joint pain (Health Canada, 2018). It may also help in exercise-induced inflammation and muscle soreness, thus enhancing recovery and performance (Hewlings & Kalman, 2017). Clinical trials indicate curcumin may have potential as a therapeutic agent in diseases such as arthritis, inflammatory bowel disease, pancreatitis, and chronic anterior uveitis, as well as certain types of cancer (Jurenka et al., 2009). Curcumin has been used either alone or in combination with other agents, and dose-escalating studies have indicated the safety of curcumin at doses as high as 8 g/day over three months (Cheng et al., 2003; Gupta et al., 2013; Madhu et al., 2013).

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.
Kobatake et al., 2021	The Long-Term Clinical Course of Canine Degenerative Myelopathy and Therapeutic Potential of Curcumin.	The results of this study suggested that the administration of curcumin is beneficial in slowing the progression of canine degenerative myelopathy.

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).

Harpagophytum procumbens (Devil's Claw) [Root]

Radix Harpagophyti is the dried secondary storage tubers of *Harpagophytum procumbens* (Burch.) DC. Ex Meisn., (Pedaliaceae). It is a ground trailing, weedy perennial about 18 inches long with a stout central taproot growing up to two meters deep. Secondary storage tubers, resembling elongated sweet potatoes, branch off horizontally. Plants of the genus owe their common name Devil's claw to the peculiar appearance of their hooked fruit. Radix Harpagophyti is widespread in the Kalahari Desert of Southern Africa. It is native to Angola, Botswana, Zambia, Zimbabwe, Namibia, Mozambique, and South Africa (AMR, 2008).

Harpagoside, harpagide, and procumbide, found in Radix Harpagophyti, are therapeutically significant constituents. Secondary storage tubers contain twice as much harpagoside as tap root (AMR, 2008). The validity of Radix Harpagophyti as an effective anti-inflammatory and analgesic preparation, particularly in the relief of arthritic symptoms, has been investigated in numerous animal, clinical and *in vitro* studies (Grant et al., 2007).

Canine studies of Radix Harpagophyti and combinations

Studies-Canine	Study Title	Study Summary
Moreau et al., 2014	A medicinal herb-based natural health product improves the condition of a canine natural osteoarthritis model: a randomized placebo-controlled trial.	In a randomized placebo-controlled trial of the canine osteoarthritis model, administration of an oral herb-based natural health product (combination of Radix Harpagophyti, Gummi Boswellii, Rhizoma Curcumae Longae, glucosamine, chondroitin sulphate, MSM, fish oil, hyaluronic acid, L-glutamine, blackcurrant) improved locomotor activity.
Manfredi et al., 2018	Effect of a commercially available fish-based dog food enriched with nutraceuticals on hip and elbow dysplasia in growing Labrador retrievers.	The study evaluated fish-based dog food supplemented with Radix Harpagophyti, Gummi Boswellii, glucosamine, chondroitin sulphate, fish oil, and green-lipped mussel powder on the development of hip and elbow osteoarthritis secondary to dysplasia, in growing Labrador retrievers during their first year of life. The study concluded that the fish-based diet with nutraceuticals has a beneficial effect on severe osteoarthritis development.

- Radix Harpagophyti is a Traditional Herbal Medicine to help relieve joint pain associated with osteoarthritis (Health Canada, 2022).

- Radix Harpagophyti is a Traditional Herbal Medicine for the relief of minor articular pain (EMA, 2016).

TOXICOLOGY

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

Undesirable effects of Radix Harpagophyti reported in human subjects (EMA, 2016):

Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal pain).
Central nervous system effects (headache, vertigo).
Hypersensitivity reactions (e.g., rash, hives, facial edema).

LD50 for harpagoside is >13.5 g/kg in mice (AMR, 2008).

The equivalent toxic dose in a 20 kg dog: >270 g of harpagoside isolated from Radix Harpagophyti.
The equivalent toxic dose in a 5 kg cat: >67.5 g of harpagoside isolated from Radix Harpagophyti.

DRUG INTERACTIONS

Radix Harpagophyti inhibits certain cytochrome P450 enzymes. Therefore, it may have an impact on drugs metabolized via these enzymes, including coumadin, antihypertensives, statins, antidiabetic agents, antiepileptics, antidepressants, and proton pump inhibitors (AMR, 2008).

Moringa oleifera (Drumstick Tree) [Seed]

Semen Moringae consists of the dried seeds of *Moringa oleifera* Lam. (Moringaceae) with high nutritional and medicinal value. It is native to India and grows in the tropical and subtropical regions of the world. All parts of the moringa tree, including the leaves, pods, flowers, and seeds, are edible. Folium et Semen Moringae has been studied for their antioxidant, anti-inflammatory, hypocholesterolemic, hypoglycemic, antispasmodic, antibiotic, and diuretic properties, as well as their importance in improving nutritional status in women, infants, and children (Gopalakrishnan et al., 2016; Perez, 2020).

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 2,000mg/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).

Saposhnikovia divaricata (Siler) [Root]

Radix Saposhnikoviae consists of dried roots of *Saposhnikovia divaricata* (Turcz. ex Ledeb.) Schischk. (Apiaceae) [syn. Ledebouriella divaricata (Turcz. ex Ledeb.) M. Hiroe] (Chen & Chen, 2004).

Phytochemical and pharmacological studies have shown that the main constituents of Radix Saposhnikoviae are chromones, coumarins, acid esters, and polyacetylenes, and these compounds exhibited significant anti-inflammatory, analgesic, antioxidant, antiproliferative, antitumor, and immunoregulatory activities (Yang et al., 2020). In traditional Chinese medicine, Radix Saposhnikoviae is the herb of choice for body aches and pain (Chen & Chen, 2004).

The administration of Radix Saposhnikoviae suppressed the development of type II collagen-induced arthritis in animal models, which may support the traditional use of Radix Saposhnikoviae in treating human rheumatoid arthritis (Wang et al., 1999).

TOXICOLOGY

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

The LD50 for aqueous extracts of Radix Saposhnikoviae in mice is 37.18 ± 8.36 g/kg (Li, 2002).

The equivalent toxic dose in a 20 kg dog: 745 g PO of Radix Saposhnikoviae aqueous extract.
The equivalent toxic dose in a 5 kg cat: 20 g PO of Radix Saposhnikoviae aqueous extract.

DRUG INTERACTIONS

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

SAFETY INFORMATION

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.
- 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.
- 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.

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