

Viscum album in Veterinary Medicine

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Abstract: *Viscum album* L., also called "Mistletoe", is a semi-parasitic plant from the European continent that grows on several host trees. This plant has a wide variety of active compounds that can be used for treating various diseases, such as diabetes, epilepsy, hypertension, among others. However, it is most indicated in human medicine for the adjuvant treatment of cancer patients. In Veterinary Medicine, very few studies record such indication for animals, although formulations for commercial use are available in oral and injectable forms, with very low doses of their active compounds. It is known that this medicine is routinely administered in clinics and veterinary offices with excellent results. In addition, it has been tested on a large scale by groups of researchers and independent clinicians in different countries, such as Switzerland, Germany, and Brazil. Therefore, this review aimed to gather data on the use of *Viscum album* within Veterinary Medicine so that there are consistent references and clear indications of its use.

Keywords: Veterinary Medicine, indications, mistletoe

1. Introduction

The use of *Viscum album* (VA) as a medicine has been described since the Celtic people, passing through the Middle Ages, and in the 19th century, it was included among the homeopathic medical matters. During this period, the *Viscum album* extracts had diversified indications and were only for oral use, which is described in the homeopathic medical matter to date. The therapeutic effects included hypoglycemic, immunomodulatory, cardiotoxic, hypotensive, hepatoprotective, antibacterial, antifungal, among others [1].

In the 20th century, the *Viscum album* extracts were cited by Rudolf Steiner (1861-1925) and Ita Wegmann (1876-1943) around 1917 with the emergence of Anthroposophical Medicine and were related to the treatment of cancer patients. The first publication on this topic is dated 1933 [2]. Steiner and Wegmann recommended that the *Viscum album* active ingredient would have to be extracted from the plant in two seasons of the year (summer and winter) to obtain the therapeutic activity more efficiently [3], considering the plant defense system and the synthesis of various substances throughout the seasons [4].

Different forms of *Viscum album* extract were prepared from the plant, such as aqueous, hydroalcoholic, ethanolic, among others [5, 6]. Pharmacological effects are usually more detectable with the administration of whole/complete plant extracts instead of purified substances, such as lectins and viscotoxins [7]. It is expected that *Viscum album* induces apoptosis and shows immunomodulatory and cytotoxic activity after administration in patients [8].

Lectins, flavonoids, phenolic acids, sterols, lignans, terpenoids, phenylpropanoids, alkaloids, fatty acids, and viscotoxins are among the active ingredients found in the plant *Viscum album*. In particular, viscotoxins can increase the amount of circulating natural killer cells and consequently improve the anti-tumor immune response of the host [9]. Similarly, viscotoxin has an effective immunomodulatory impact on human and animal granulocytes [10, 11] and also acts on cellular apoptosis

[12]. The cytotoxic action of viscotoxin is comparable to that from conventional chemotherapy agents [13].

Within this context, very few studies in Veterinary Medicine record such indication for animals, even though formulations for commercial use are available with extremely low doses of their active compounds. *Viscum album* is routinely administered in clinics and veterinary offices with excellent results, and it has been tested on a large scale by groups of researchers and independent clinicians in countries such as Switzerland, Germany, and Brazil.

The use of homeopathic medicines prepared from plant extracts, which have been experimentally studied in Brazil and other countries, is thereby highlighted [14, 15]. However, according to classical homeopathic pharmacopeia, no data is found in the literature on the effects of prepared *Viscum album*. These commercial formulations of homeopathic *Viscum album* are available on the market for years and present very low doses of their active ingredients [16]. Published experimental studies provide specific information on the mechanisms of action of this medicine in tumor or immune system cells, but the cytotoxic, apoptotic, and immunological aspects of *Viscum album* are not demonstrated in the studies [17].

Nevertheless, studies with *Viscum album* extracts have increased in quantity and quality in the last five years, particularly within Veterinary Medicine. Thus, this work aims to report the main studies performed within this area, explaining all the functions of this medicine regardless of the administration form, which is basically comprised of the oral and injectable forms.

2. Literature Survey

Reports on the use of the *Viscum album* therapy within Veterinary Medicine began to be systematically identified from 1979 when Petkov started using these extracts intravenously and obtained satisfactory results in controlling blood pressure in dogs [18]. Throughout history, the *Viscum album* therapy has been successfully administered to cancer patients in various animal species

[19]. Additionally, Bowman [20] confirmed the hypotensive activity of *Viscum album* extracts when intravenously given to dogs and emphasized its beneficial cardiovascular effects on these animals.

Among the various properties of the *Viscum album* plant, the most outstanding are anticancer, cardiotoxic, antidiabetic, hepatoprotective, antioxidant, antibacterial, antifungal, and immunomodulatory activities. The latter has been described since the beginning of the 19th century in humans. In animals, the immunomodulatory activity of the *Viscum album* extract (Iscador[®]) was recorded when it was subcutaneously and intravenously applied in rabbits, influencing the immunological parameters in an "in vivo" experiment [21]. This medicine significantly increased lymphocyte synthesis, especially the natural killer and phagocytic activity of granulocytes. The changes in these parameters were also determined in human cancer patients after the application of *Viscum album* (Iscador[®]) extracts, emphasizing the relevance of lectin in the extracts. Therefore, these results encourage studies in this area [21].

The hypoglycemic properties of the *Viscum album* extracts were described by Ohiri et al. [22]. The study reported the control of glycemia in diabetic animals induced by alloxan. The experiment included administering doses of 200 mg/kg and 400 mg/kg body weight that significantly reduced blood sugar in fasted normal albino rats and alloxanized rabbits, respectively. Fasting blood sugar, measured in milligrams per 100 mL, was reduced by 30.06% in normoglycemic rats, whereas in alloxanized rabbits, blood sugar was reduced from the mean value of 650 ± to 7.2 mg% in zero-hours to 87 ± 8.2 mg% at 4h. The hypoglycemic effects were compared to those of tolbutamide. Acute toxicity studies of the extract in mice showed LD₅₀ value of 4.18 ± 0.96g/kg body weight when given intravenously.

In 2008, Klocke et al. [23] pointed out that there are positive results in administering the *Viscum album* therapy in animals. However, there is a lack of scientific data on the efficacy of the therapy in this area. For this reason, the authors performed two studies to evaluate if the *Viscum album* (Iscador[®]) extracts could serve as a complement to the standard treatment in cats and horses. The experiment comprised a double-blind study controlled by placebo (Study 1), totaling 53 horses diagnosed with sarcoid. The horses were treated subcutaneously with increasing doses of *Viscum album* (n=32) or sodium chloride solution (n=21) three times a week over 15 weeks. All horses were evaluated for 12 months regarding the disease recurrence and/or total cure of the tumor. In another observational study (Study 2), 44 cats with fibrosarcoma, neoplasia considered with a high recurrence rate, were orally treated in the postoperative period with *Viscum album* 0.1% (0, 5 mL/dose) two times a day. Survival and disease recurrence rates were evaluated. As a result, the treated group showed significantly better responses than the control group in Study 1. Improvement in symptoms was observed in 41% of the cases (placebo: 14%), and cure was achieved in 28% of the cases (placebo 14%). In Study 2, the survival of the disease-free cats treated postoperatively with *Viscum album* was 438 days compared with 365-475 days for

conventional chemotherapy and 120-261 days for surgery alone. Aggressive surgery combined with radiation and chemotherapy resulted in superior survival (661-986 days). Furthermore, human literature showed that when *Viscum album* and conventional therapies are combined, survival is increased, and the quality of life of patients undergoing this type of therapy is improved compared with patients on single therapy [23]. Therefore, Study 1 shows that the subcutaneous administration of *Viscum album* preparations also produces satisfactory prophylactic effects. For the first time, the second study demonstrated the *Viscum album* efficacy compared with control and placebo in animals. This study also showed that the effect of *Viscum album* extracts apparently extends beyond the treatment period. Only a few recurrences were recorded between the end of treatment and the 12th month of evaluation [23].

Blostinand Faivre [24] recorded more promising results than those from Klocke et al. [23] and demonstrated the benefits of oral fermented *Viscum album* in cats after surgical resection of fibrosarcoma tumor. In this multicentric study of 22 cats, the treatment was well accepted and tolerated, and no side effects were observed. The authors concluded that the treatment appeared to be at least as effective as the best current conventional treatment (radiotherapy). The mean survival time was 65.4 months, and the mean disease-free interval was 53 months. These findings contrast with Klocke et al. [23], who stated that conventional therapy showed better results with the administration of single conventional therapy and survival of approximately three years. In the study performed by Blostinand Faivre [24], the survival of animals treated with the *Viscum album* therapy was almost twice as long, about five years.

Christen-Clottu et al. [25] conducted an experiment with 53 horses clinically diagnosed with sarcoid and used *Viscum album* extracts as a treatment. Forty-two animals were treated with *Viscum album* extracts or placebo as monotherapy; 11 animals were treated with *Viscum album* or placebo after selective sarcoid excision. Prospective, randomized, blinded, clinical trial. Horses were randomly assigned to treatment (*Viscum album* n = 32) or control group (Placebo n = 21). One millimeter of *Viscum album* extract (Iscador[®]) in increasing concentrations from 0.1 to 20 mg/mL or physiological solution of NaCl was given subcutaneously three times a week for 105 days. Number, location, and type of sarcoid were documented over 12 months. In conclusion, the authors reported that no unwanted adverse effects were observed during the experiment, except for mild edema at the injection site in five of 32 horses (16%). Complete or partial regression was observed in 13 horses of the group treated with *Viscum album* (41%) and in three of the control horses (14%; P < 0.05). After treatment with the *Viscum album* extracts, 48 of 95 sarcoid lesions (67%) showed an improvement compared to 17 of 68 equine sarcoid lesions in the control group (40%; P < 0.01). Twenty-seven equine sarcoid lesions disappeared completely in the group treated with *Viscum album* extracts (38%) compared to nine equine sarcoid lesions in the control group (13%). Based on these results, *Viscum album* (Iscador[®]) extracts

represent a safe and effective treatment for lesions caused by equine sarcoid.

Biegel et al. [26] described the use of *Viscum album* (Iscador®) extracts for the successful management of skin neoplasms in cats regarding relevant aspects to human medicine. The study aimed to evaluate the prophylactic effects of oral administration of *Viscum album* in cats after surgical excision of the tumor, assessing the overall and disease-free survival. A total of 44 cats diagnosed with fibrosarcoma were studied. After surgical excision, the animals received 0.5 mL of a 1mg/mL aqueous dilution (Iscador®) twice a day. The median survival time was 438 days (95% CI, 222 days), approximately 14 months. More than 50% of the animals operated in Clinic 1 survived with no disease associated with the occurrence of fibrosarcoma. Cats operated in Clinic 2 (presumably with a higher disease progression) showed a median survival time of 250 days. Although lacking a control group in this study, it can be concluded that post-surgical oral *Viscum album* preparations may lead to results similar to those achieved after post-surgical chemotherapy in cases of fibrosarcoma. According to the author, the results may be promising, especially in cats treated in ordinary veterinary practice, due to the owner's unwillingness to pay for radical treatment.

Regarding the safety of the *Viscum album* therapy administration in animals and humans, Kienle et al. [27] conducted a review that included data collection on the *Viscum album* application in high dosages aiming at its immunological parameters and safety. No indication of immunosuppression was found in the animal experiments (n=48) and clinical studies (n=69) investigating higher dosages of *Viscum album*. Most studies reported an explicit immunostimulation, even at high dosages of *Viscum album*. As the review investigated an extensive range of dosages, treatment and evaluation periods, and important parameters, the authors considered clinically relevant immunosuppression to be unlikely. Side effects observed during the treatment with *Viscum album* at high dosages generally consisted of local reactions, flu-like symptoms, non-specific effects, allergic or pseudo-allergic reactions in some cases. The *Viscum album* therapy was considered safe for normal application. Kienle et al. [27] concluded that it could also be considered low risk when used for local or systemic application at high dosages if monitored by an experienced physician or veterinarian in this therapy.

Carvalho et al. [28] reported administering the *Viscum album* medicine in its injectable presentation, manufactured according to the German homeopathic pharmacopeia, for the first time in history. The medicine was used in a 10-year-old female dog, Labrador breed, diagnosed with malignant neurofibrosarcoma, showing positive markers for vimentin and CD57, and negative for protein S100, GFAP, AC4, Desmin, and CD31. Ultrasound imaging showed an increased liver mass. Adrenal glands revealed nodular hyperechogenic areas with smooth contours. The treatment was performed with the commercial medicine *Viscum album* (Injectecenter®), at predetermined potencies, given as follows: 1st day: D3

(1X10⁻³) + D6 (1X10⁻⁶); 2nd day: D9 (1X10⁹) + D12 (1X10¹²); 3rd day: D30 (1X10⁻³⁰) + D3; 4th day: D6 + D9; 5th day: D12 + D30; 6th day: D3 + D9; 7th day: D12 + D6; 8th day: D9 + D30; 9th day: D12 + D3; 10th day: D6 + D30, prescribed once a day, subcutaneously, in a series of five days of treatment and one day free from treatment between each series. The total treatment time was 30 days. The neoplasm ceased its growth and showed a slight decrease, which was regularly visualized by imaging - ultrasonography [28].

In a retrospective study, Glardon et al. [29] demonstrated the clinical safety of *Viscum album* (Iscador®) regarding its side effects and possible indications when given subcutaneously. Twenty-two cats treated between 2008 and 2013 were evaluated, four of which did not accept the applications made by the tutors, and seven had mild short-time adverse reactions that disappeared spontaneously. No long-term (more than 70 days) adverse reaction directly related to the *Viscum album* treatment was observed, and no other reactions were identified. This study demonstrated that *Viscum album* extracts could be applied subcutaneously with no risk of worsening clinical signs or exacerbation of tumors. According to these authors, its anti-tumor, immunomodulatory, and anti-inflammatory properties offer attractive treatment opportunities for cancer or allergic patients.

Carvalho and Bonamin [16] performed a systematic review of the *in vitro* and *in vivo* models described in the literature, including veterinary clinical trials. They found several types of pharmaceutical preparations of *Viscum album* and its active principles used in experimental studies. Among the *in vivo* experimental studies on *Viscum album* and its compounds, the B16 murine melanoma is the most used model, followed by the Ehrlich, Walker, and Dalton tumors. The results pointed to apoptotic effects, metastasis control, and tumor regression. Some veterinary clinical studies on the use of *Viscum album* to treat sarcoid [25], fibrosarcoma [26], and neuroblastoma [28] are also cited in the literature with interesting results. Regarding the *in vitro* models, Carvalho and Bonamin [16] also recorded that NALM6 leukemia cells, B16 melanoma, and NC1-H460 lung carcinoma were the most studied tumor models. The authors concluded that there is a marked lack of information on the effects of homeopathic preparations of this plant on animal tumors and tumor cells.

Also, Turkkan et al. [30] demonstrated the activity of *Viscum album* extracts in a conventional experimental rat model with streptozotocin (STZ)-induced diabetes to evaluate the effects of this medicine on lipid peroxidation and antioxidant system. The experiment was performed with 32 adult rats divided into four groups of eight rats each: Group – control (STZ); Group 2 - tested 1 (VA); Group 3 - tested 2 (VA + STZ). The *Viscum album* extract was orally given for ten days. Fasting blood glucose level was measured and recorded. The animals were sacrificed, and catalase (CAT), malondialdehyde (MDA), and proteins present in liver and kidney tissue samples were measured. After statistical analysis, it was found that oxidative stress was associated with diabetic complications. The *Viscum album* extracts given to

diabetic rats reduced oxidative stress and improved their overall condition. However, despite the promising results obtained in this work, the authors stated that further studies are needed to increase the understanding of potential antidiabetic and antioxidant effects of the *Viscum album* therapy.

Biegel et al. [19] report that canine mammary tumors are still challenging veterinary medicine due to their enormous sample. Within this context, they suggest the therapy with *Viscum album* extracts, an adjuvant therapeutic method widely used in human cancer patients, which could be of great value to veterinary patients. Their study demonstrated the effect and benefit of postoperative *Viscum album* therapy as an adjuvant tool for female dogs with mammary tumors. The effects of the therapy on the patients' quality of life during treatment were also evaluated. Fifty-six female dogs with mammary adenocarcinoma were enrolled in the study; 33 dogs served as the control group and were operated exclusively; 23 dogs were operated and received adjuvant *Viscum album* therapy. At the end of the study, the authors concluded that the mean survival time of all animals (n = 56) was 32 months, with an interquartile range between 13-51 months. In the descriptive comparison of survival times according to Kaplan-Meier, the control group showed survival of 24 (72.7%), 20 (60.6%), 15 (45.1%), and 5 (12.4%) dogs after 12, 24, 36, and 48 months, respectively. In the group tested with *Viscum album*, survival was 19 (82.6%), 14 (60.9%), 11 (47.8%), and 1 (4.3%), respectively. Lower overall death risk was recorded after the *Viscum album* therapy. However, it was not statistically significant between treatments (hazard ratio (HR) 0.530, 95% confidence interval (CI) 0.222-1.262; p = 0.15). Additionally, a not significant (p = 0.07) tendency of reduction in tumor-related death risk to 25% (HR 0.251, 95% CI 0.056-1.122) was recorded. As an outcome of this study, Biegel et al. [19] revealed a trend towards reducing the risk of tumor-related mortality in the tested group, assuming that the patients well tolerated the therapy. The animals' quality of life remained stable at a high level during the observation period.

Von Bodungen et al. [31] described the treatment of oral melanomas in dogs using the *Viscum album* therapy. The study evaluated the feasibility of *Viscum album* therapy as a therapeutic option for this disease. Special attention was given to survival time and possible side effects. Twenty-six dogs diagnosed with oral melanoma and that received radiotherapy in one of Switzerland's largest veterinary cancer centers were included in the retrospective study. Eighteen dogs were treated with *Viscum album* (Iscador[®]) in increasing concentrations from 0.1 to 20 mg/mL subcutaneously three times a week (VA group); eight dogs did not receive any adjuvant treatment (control group). The development of oral melanoma size was compared to survival time. The results indicated that patients with radiation and *Viscum album* therapy had a significantly longer median survival time of 236 days than patients with radiation and no *Viscum album* therapy (49 days). The *Viscum album* therapy increased survival time by more than two-thirds. In its turn, according to the UICC (Union for International Cancer Control), a higher tumor stage

showed a statistical trend towards doubling the death risk. Two patients experienced mild side effects during treatment with *Viscum album*. One of them had a self-limited fever for one day. In the other patient, the more concentrated *Viscum album* dosage was reduced to a less concentrated one due to fatigue, which then disappeared. This study concluded that the *Viscum album* therapy is a safe treatment with few side effects and positively affects the survival time of dogs with oral melanoma. Therefore, this therapeutic approach is worthwhile to be considered for treating this pathology. However, the groups compared were small, diverse, and inconsistent concerning all prognostic parameters. For this reason, Von Bodungen et al. [31] stated that it would be interesting to perform a prospective work with a larger study population.

Recently, Valle et al. [32] and Valle and Carvalho [33] report the treatment of cutaneous melanoma with the *Viscum album* therapy in dogs and corroborated Von Bodungen et al. [31]. However, both Valle et al. [32] and Valle and Carvalho [33] used *Viscum album* injectable extracts, manufactured according to the homeopathic pharmacopeia, in the following potencies: D3, D6, D9, D12, and D30 (Injectcenter[®]). The medicines were chosen by anatomopathological similarity, following the principles of homeopathy. In both studies mentioned above, the patients had satisfactory results in their treatments. Valle et al. [32] recorded the resolution of the initial complaint, and Valle and Carvalho [33] reported longer survival, with no metastasis or disease recurrence within two years.

Valle et al. [34] described the treatment of a 12-year-old female mixed breed dog diagnosed with myeloma in the lumbar spine. The diagnosis was performed by histopathological examination and confirmed by immunohistochemistry. The patient was treated subcutaneously with the homeopathic medicine *Viscum album*, using the following potencies in different combinations: D3, D6, D9, D12, and D30 (Injectcenter[®]). The authors reported satisfactory results and more prolonged survival, considering the mean survival time observed for this type of neoplasm. Similarly, Lopes et al. [35] reported the treatment of canine lymphoma by subcutaneous applications of homeopathic *Viscum album* in combined potencies D3, D6, D9, D12, and D30 (Injectcenter[®]). Their results also showed improvement in the patient's quality of life and increased survival. Therefore, these studies demonstrated the clinical effectiveness of *Viscum album*.

In another study, Valle et al. [36] recorded the use of ultra-diluted *Viscum album* for treating transmissible venereal tumor (TVT) in a mixed breed dog. The 2-year-old patient diagnosed with TVT was orally treated with *Thuya occidentalis* D12 (1×10^{-12}); topical application of *T. occidentalis* D9 (1×10^{-9}) in the lesion; and subcutaneous applications of *Viscum album* in different combinations, in the D3, D6, D9, D12, and D30 potencies (Injectcenter[®]). The tumor was reduced by about 90% during 150 days of treatment, and the patient no longer had bloody vaginal discharge or discomfort when urinating. Complete remission was achieved with a single application of vincristine ($0.025 \text{ mg} \cdot \text{Kg}^{-1}$). No complications were

observed one week later, and cytological examination confirmed the absence of tumor cells. No side effects were observed during the entire treatment period. Thus, the *Viscum album* therapy was effective in its purpose.

Bello et al. [37] studied the antidiabetic activity of the aqueous leaf extract of *Viscum album*, *in vivo*, and compared its antidiabetic efficacy against the drug metformin. Biochemical analysis demonstrated a significant dose-dependent reduction ($P < 0.05$) in serum glucose levels in rats when treated with *Viscum album* leaf extract. This result was observed when groups treated with *Viscum album* were compared to the diabetic control and metformin-treated groups. Likewise, there was a significant decrease in the levels of total cholesterol, triglycerides, and low-density lipoproteins that were elevated before the treatment with the leaf extract. A correspondingly significant increase in high-density lipoprotein levels was observed when compared to the diabetic control group. The plant extract significantly reduced ($P < 0.05$) the serum activities of the marker enzymes: Alanine and Aspartate aminotransferases. Similarly, a significant reduction ($P < 0.05$) was detected in creatinine and urea levels in the groups treated with *Viscum album* extract and metformin compared to the diabetic control group. Moreover, the plant extract attenuated the weight loss recorded in the diabetic control group. Aqueous leaf extract of *Viscum album* demonstrated high antidiabetic activity, which is compared with metformin.

Halo et al. [38] went beyond the indications available for the medicine and tested the effects of *Viscum album* (Iscador[®]) extracts on rabbit spermatozoa motility and viability *in vitro*. The results suggest a negative effect on spermatozoa motility and viability parameters *in vitro*, which is dependent on the dosage and exposure time to the *Viscum album* extract at higher dosages. However, the differences were not significant. Significant changes in membrane integrity were found in the groups with the highest concentration of *Viscum album*, but acrosome integrity had no significant changes.

In a recent study, Valle et al. [39] reported treating a female dog with cholangiocarcinoma by integrative therapy with ultra-diluted *Viscum album*. The neoplasm was inoperable, and the only possibility was the clinical treatment. In addition, the patient had pulmonary and splenic metastasis. The animal was treated with ultra-diluted *Viscum album*, which was given subcutaneously and intravenously in the D3, D6, D9, D12, and D30 potencies (Injectcenter[®]) for 11 months. The authors stated that the *Viscum album* administration improved the animal's quality of life and decreased the growth rate of the tumor. In addition, it significantly increased the patient's survival time, ceasing the growth of pulmonary and splenic metastases, which were accompanied regularly by chest x-ray and abdominal ultrasounds.

Valle [17] evaluated the safety potential of commercial subcutaneous and intravenous applications of *Viscum album* D3 (Injectcenter[®]) in dogs weighing between 2 and 5Kg, from 4 to 8 years. The animals underwent previous

evaluation consisting of physical examination and laboratory tests (leishmaniasis, ehrlichiosis, Lyme disease, anaplasmosis, heartworm disease, complete blood count, and biochemical dosages of urea, creatinine, alanine aminotransferase, and alkaline phosphatase). Blood tests were performed twice a week for three weeks in addition to weekly questionnaires that the tutors answered regarding the animals' quality of life/welfare during the administration of the medicine. After the experiment period and analyses of exams and statistical tests, the author concluded that there was a transient increase in the number of monocytes ($P = 0.0022$) at day 5, while there was no significant ($P > 0.05$) change in any of the other blood endpoints over time. Nevertheless, all blood parameters remained within the reference values for the species. All animals completed the study in good health conditions. According to the Quality of Life Assessment Questionnaire, all animals showed improvement in mood and appetite after receiving VAD3. The homeopathic medicine VAD3 is safe for intravenous and subcutaneous applications in dogs, possibly bringing benefits to the entire organism.

In 2021, Carvalho and Valle [40] described the treatment of Alimentary Lymphoma in the stomach fundus region of an 11-year-old Siamese cat, negative for FIV/FeLV, using the homeopathic *Viscum album*. Endoscopy was performed associated with biopsy to determine the diagnosis. The biopsy result was suggestive for lymphoma; immunohistochemistry was conclusive for lymphoblastic lymphoma with immunophenotype B. The treatment established comprised the *Viscum album* (Injectcenter[®]) therapy associated with the homeopathic medicine *Magnesia phosphorica* (Injectcenter[®]). The applications were performed daily for 120 days. After this period, new imaging tests (ultrasound and endoscopy) were done, as well as biopsy and histopathology, demonstrating the total resolution of the disease. Therefore, the treatment was effective and restored the patient to health, who lived for almost two years and died from causes not related to cancer.

Valle and Carvalho [41] described a case of lymphoma in a 4-year-old mixed breed male cat, positive for FIV/FeLV. The patient was successfully treated by homeopathy with subcutaneous applications of *Viscum album* D3, D6, D9, D12, and D30 (Injectcenter[®]), *Arnica montana* D10 (Injectcenter[®]), *Apismelifera* D30 (Injectcenter[®]), and *Mercurius solubilis* 30CH (Injectcenter[®]). After completing the treatment period, the lesion was completely healed, and the animal remained well for 36 months until he died from causes unrelated to lymphoma. The authors concluded that the treatment used allowed the complete resolution of the disease with no side effects on the patient. Moreover, the patient's life expectancy was increased.

Another recent work from Valle and Carvalho [42] reported that the *Viscum album* therapy is also indicated to treat cancer patients when conventional medicine is not an option to be considered, such as inoperable tumors, as well as in Palliative Care, aiming to maintain the patient's quality of life. Under this perspective, the authors described the healing process of a lesion of difficult

resolution due to a squamous cell carcinoma (SCC) in an advanced stage in a 9-year-old female dog of white fur, PitBull breed. The disease was treated with the ultra-diluted *Viscum album* (Injectcenter®). The patient responded favorably and rapidly to the prescribed treatment showing complete healing of the lesion derived from an SCC in only four weeks. Enhanced appetite and overall disposition were also observed, evidencing the improvement in the patient's quality of life despite the advanced stage of the disease.

Within this context, Valle and Carvalho [43] reported the treatment and cure of a 16-year-old female dog, Maltese breed, diagnosed with oral SCC. The patient was treated using the homeopathic *Viscum album* D3 (Injectcenter®) medicine, based on alternate day protocol. The patient was completely recovered within 30 days. The lesion disappeared from the upper lip, and the cure of the disease was confirmed months later by incisional biopsy. Given the patient's advanced age, she died from non-related SCC

causes (acute renal disease) 14 months after the SCC diagnosis.

Valle and Carvalho [33] also described the *Viscum album* therapy administration in a female dog with an ulcerated lesion in the fourth digit of the right anterior leg caused by cutaneous melanoma. The animal was previously treated by chemotherapy and did not present clinical improvement of the condition, remaining nine months with no treatment. After this period, the *Viscum album* D3 (Injectcenter®) treatment was started and consisted of intravenous and subcutaneous applications of the medicine. The patient also had two evolving mammary tumors, several blackish nodular lesions spread throughout the body, and pulmonary metastasis. Despite the well-advanced stage of the disease, the protocol administered to the patient was successful in its purpose. It healed all ulcerated lesions presented by the patient and significantly improved her quality of life.

Table 1: Experiments in animal species with *Viscum album* extracts, activity, administration route, and extract origin.

Year	Author	Species	Activity	Administration route	Medicine
1979	Petkov [18]	Canine	Antihypertensive	Intravenous	Iscador®
1989	Hajto et al. [21]	Rodent	Immunomodulation	Subcutaneous/Intravenous	Iscador®
1990	Bowman [20]	Canine	Antihypertensive	Intravenous	Iscador®
2003	Ohiri et al. [22]	Rodent	Hypoglycemic	Intraperitoneal	Own extract
2008	Klocke et al. [23]	Equine	Sarcoid	Intravenous	Iscador®
2008	Klocke et al. [23]	Feline	Fibrosarcoma	Oral	Iscador®
2008	BlostinandFaivre [24]	Feline	Fibrosarcoma	Oral	Iscador®
2010	Christen-Clottu et al. [25]	Equine	Sarcoid	Subcutaneous	Iscador®
2011	Biegel et al. [26]	Feline	Fibrosarcoma	Oral	Iscador®
2011	Kienle et al. [27]	Canine	Safety	Subcutaneous	Iscador®
2013	Carvalho et al. [28]	Feline	Neurofibrosarcoma	Subcutaneous	Injectcenter®
2014	Gardon et al. [29]	Feline	Safety	Subcutaneous	Iscador®
2015	Carvalho [44]	Rodent	Ehrlich Tumor	Intraperitoneal	Injectcenter®
2016	Turkkan et al. [30]	Rodent	Hypoglycemic	in vitro	Own extract
2017	Biegel et al. [19]	Canine	Mammary Tumor	Subcutaneous	Iscador®
2017	Von Bodungen et al. [31]	Canine	Oral Melanoma	Subcutaneous	Iscador®
2018	Valle et al. [34]	Canine	Myeloma	Subcutaneous/Intravenous	Injectcenter®
2018	Lopes et al. [35]	Canine	Lymphoma	Subcutaneous	Injectcenter®
2019	Bello et al. [37]	Rodent	Hypoglycemic	Oral	Own extract
2019	Valle et al. [36]	Canine	Transmissible Venereal Tumor	Subcutaneous	Injectcenter®
2019	Biegel et al. [45]	Canine/Feline	Melanoma/Mammary tumor	Subcutaneous	Iscador®
2020	Valle et al. [32]	Canine	Cutaneous Melanoma	Subcutaneous	Injectcenter®
2020	Valle et al. [39]	Canine	Cholangiocarcinoma	Subcutaneous/Intravenous	Injectcenter®
2020	Valle [17]	Canine	Safety	Subcutaneous/Intravenous	Injectcenter®
2021	Carvalho andValle [40]	Feline	Alimentary Lymphoma	Subcutaneous	Injectcenter®
2021	Valle andCarvalho [33]	Canine	Cutaneous Melanoma	Subcutaneous/Intravenous	Injectcenter®
2021	Valle andCarvalho [41]	Feline	Lymphoma	Subcutaneous	Injectcenter®
2021	Valle andCarvalho [42]	Canine	Squamous Cell Carcinoma	Subcutaneous/Intravenous	Injectcenter®
2021	Valle andCarvalho [43]	Canine	Oral Squamous Cell Carcinoma	Subcutaneous/Intravenous	Injectcenter®

3. Conclusion

The oral administration of *Viscum album* has been known for centuries by popular medicine, especially in the European continent, with indications for patients with heart disease, hypertension, diabetes, among others. The injectable *Viscum album* therapy has been used by human medicine for more than 100 years for treating cancer patients, based on the indications of Steiner and Vegman.

Given the above mentioned in this review, it is evident the considerable evidence of the pharmacological and safety activities of the *Viscum album* extracts, whether manufactured according to the homeopathic pharmacopeia (Injectcenter® - Brazil) or by anthroposophy (Iscador® - Switzerland). It also should be emphasized that the *Viscum album* therapy must be administered by qualified professionals and with clinical experience in this therapy. Furthermore, this review summarized most existing studies

on the application of *Viscum album* extracts in animals, whether *in vivo* or *in vitro*, and the following topics were approached: safety of *Viscum album* administration for animals, its possible direct beneficial effects on quality of life, the palliative care of patients in an advanced stage of the disease, in inoperable tumors, and in situations in which conventional treatments are not beneficial. Based on the data exposed in this review, *Viscum album* is a potential alternative for aiding in the treatment of various diseases in animals. However, its use in Veterinary Medicine is a new field for clinical and laboratory research. Therefore, more studies are needed on the real *Viscum album* potential, its impact on the quality of life of veterinary patients, mechanisms of action, metabolism, among others.

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