

## Review of mistletoe literature from the 2nd half of 2024

### Botany

**Adenekan T: Exploring the characteristics and ecological impact of common mistletoe (*Viscum album*) in forest management. Online Publication 2024:** Mistletoe (*Viscum album*), a semi-parasitic plant species widespread in Europe and parts of Asia, plays a complex role in forest ecosystems. On the one hand, it can cause damage to host trees due to its semi-parasitic character; on the other hand, mistletoe also contributes to biodiversity by providing habitat and food for various animal species. This article therefore describes how the ecological benefits of mistletoe can be harmonised with the need to protect the health and productivity of the forest.

**Deconninck G, Boulembert M, Eslin P et al.: Environmental factors driving infestations of a key-stone winter fruit by an invasive and a native fruit fly. Arthropod-Plant Interactions 2024;18:867-880:** The aim of this study was to investigate the effects of climatic, landscape-specific and regional factors on the infestation rate of mistletoe fruits (*Viscum album*) by *Drosophila* flies in winter. The fruits were used as a food source by both the invasive *Drosophila suzukii* and the native *Drosophila subobscura* in the second half of winter and in spring, which could help these species to bridge the winter food bottleneck. The occurrence of both fly species was closely linked to the presence of mistletoe fruit that had fallen to the ground and to semi-natural (forest, hedges) and anthropogenic habitats (garden, park).

**González de Andrés E, Gazol A, Querejeta JI et al.: Mistletoe-induced carbon, water and nutrient imbalances are imprinted on tree rings. Tree Physiology 2024;44:pp 17. <https://doi.org/10.1093/treephys/tpae106>:** To improve the understanding of physiological responses to mistletoe and ongoing climate change, radial growth, stable carbon and oxygen isotopic signals, and elemental composition of tree rings in silver fir (*Abies alba* Mill.) and Scots pine (*Pinus sylvestris* L.) forests infested with *Viscum album* L were investigated. For this purpose, time series (1990-2020) of basal area increment (BAI), intrinsic water-use efficiency (iWUE), oxygen isotope composition ( $\delta^{18}\text{O}$ ), nutrient concentrations and stoichiometric ratios were compared between non-infested (NI) and severely infested (SI) fir and pine from populations in north-eastern Spain. The SI trees showed historically higher growth, but the BAI trend was negative for more than three decades before 2020 and their growth rates became significantly lower than those of NI trees by the mid-2010s. The SI trees showed historically higher growth, but the BAI trend was negative for more than three decades before 2020 and their growth rates became significantly lower than those of NI trees by the mid-2010s. Also, the SI trees showed lower iWUE values than the NI trees, which together lead to a gradual occurrence of carbon, water and nutrient imbalances in mistletoe-infested conifers in seasonally dry regions.

**Ramm H: Was Misteln erfolgreicher macht (What makes mistletoe more successful). Flächenmanager 2024;4: 44-47:** For the spread of mistletoe and its regulation, it is important to know its biology, i.e. how and in which conditions mistletoe can spread particularly successfully. For example, warmth as a result of climate change indirectly promotes the expansion of mistletoe by increasing the habitat of mistletoe-spreading birds such as blackcaps, which have adapted their migration behaviour to the milder winters in recent decades and prefer to spend the winter where they can find enough mistletoe berries. They therefore play an important role in the widespread distribution of mistletoe.

**Reisch B: Mistelbekämpfung im Realteilungsgebiet (Mistletoe control in a real division area). Obst & Garten 2024;7:28-30:** As mistletoe infestation on apple trees in meadow orchards is increasing significantly, a community in Baden-Württemberg (Enzkreis) started an initiative to contain the spread of mistletoe in a sustainable manner in the area. The aspects of species protection are also taken into account, as mistletoe control in meadow orchards is a balancing act between sustainable mistletoe removal, preservation of uninfested trees and reduction of infestation on the one hand, and tree-friendly work with preservation of habitat structures on the other. In practical realisation, progress can therefore only be made with compromises and a pragmatic approach, such as the professional

removal of mistletoe depending on its stage of development, its position in the tree and the degree of tree infestation, as it is not possible to satisfy all aspects equally.

## Biology

**Schröder L, Senkler J, Braun HP: The energy metabolism of European mistletoe (*Viscum album* L.). In: Scheer R, Alban S, Beer AM et al. (Hrsg.): Die Mistel in der Tumorthherapie 6. Aktueller Stand der Forschung und klinische Anwendung. KVC-Verlag Essen 2024;6:35-44:** The mistletoe plant has an extremely large genome with almost 100 billion base pairs (nucleotide pairs) and the nucleotide composition of the protein-coding genes is unusual for dicotyledonous plants, as the proportion of nucleotides deoxyguanosine monophosphate (G) and deoxycytidine monophosphate (C) is comparatively high. This implies an increased DNA stability, but at the same time a considerably higher energy requirement for the transcription of their genes. Cell division also requires a great amount of energy, as the genome must first be duplicated. However, it has been shown that mistletoe can live with a comparatively reduced energy metabolism despite the increased energy requirement for its genetic system. This suggests that the host trees must supply the mistletoe with energy-rich compounds to a greater extent than previously thought.

## Biochemistry/Chemistry

**Ciftci B, Karaman K, Kaplan M: Comparison of antioxidant, antiradical and antibacterial activities of mistletoe (*Viscum album* L.) fruits and leaves growing on different host tree genus. Waste and Biomass Valorization 2024;15: 2819-2832:** To compare the bioactivity and antibacterial activity of mistletoe fruits and leaves from different host trees (robinia, wild pear, pine, hawthorn, willow, apricot and almond), their fruits and leaves were removed and the most suitable solvent for extraction was determined. It was 92.5 per cent ethanol and 7.5 per cent water for the fruit extraction and 30 per cent ethanol and 70 per cent water for the leaf extraction. The results showed significant differences depending on the tree species, with the highest antioxidant and radical scavenging activities observed in robinia mistletoe and the lowest in willow mistletoe. In terms of antibacterial activity, the highest inhibition rate for *Salmonella typhimurium* was obtained with the extract from wild pear leaves. Mistletoe leaf extracts showed a remarkable superiority bioactive performance than those of the mistletoe fruits for all tree species.

## Preclinic

### Cell cultures

**Lyu SY, Meshesha SM, Hong CE: Synergistic effects of mistletoe lectin and cisplatin on triple-negative breast cancer cells: insights from 2D and 3D *in vitro* models. Int. J. Mol. Sci. 2025;26:366. <https://doi.org/10.3390/ijms26010366>:** In this study, the potential synergistic effects of Korean mistletoe lectin (*Viscum album* L. var. *coloratum agglutinin*, VCA) and cisplatin on the MDA-MB-231 cell line (for triple-negative breast cancer, TNBC) were investigated in 2D and 3D culture models. In 2D cultures, the combination of VCA and cisplatin synergistically inhibited cell proliferation, induced apoptosis and arrested the cell cycle in the G2/M phase. In addition, the combination treatment significantly reduced cell migration and invasion. Gene expression analysis showed significant changes in specific genes associated with apoptosis, metastasis and epithelial-mesenchymal transition (EMT). The combination treatment also reduced the expression of the angiogenesis-related factors VEGF-A and HIF-1 $\alpha$ . The 3D models showed different drug sensitivity compared to the 2D cultures, emphasising the importance of using physiologically relevant models in preclinical cancer research.

**Wolfshöfer S, Gast M, Schad F et al.: Inhibition of colorectal cancer cell line growth by mistletoe extracts. In: Scheer R, Alban S, Beer AM et al. (Hrsg.): Die Mistel in der Tumorthherapie 6 – Aktueller Stand der Forschung und klinische Anwendung. KVC-Verlag Essen 2024;6:91-101:** To investigate the influence of the two different mistletoe extracts Helixor A (fir mistletoe) and Helixor M (apple tree mistletoe) on the cell viability of six different colorectal carcinoma cell lines (Caco2, HT-29, SW48, SW480, HCT116, p53-mutated HCT116), the mean inhibitory concentration was determined after 72

hours of treatment. Both mistletoe extracts reduced the cell viability of colorectal carcinoma cell lines in a dose-dependent manner. Helixor A extracts were more effective than Helixor M extracts in all six cell lines analysed. Compared to cells treated with 5-fluorouracil alone, the additional treatment of SW480 cells with mistletoe extract reduced cell viability by approx. 50 per cent and Caco2 cells by approx. 30 per cent, indicating an additive effect of the mistletoe extract.

**Zilkowski I, Turek C, Mörbt N et al.: *In vitro* mutagenicity assessment of aqueous *Viscum album* L. preparations. In: Scheer R, Alban S, Beer AM et al. (Hrsg.): *Die Mistel in der Tumorthherapie 6 – Aktueller Stand der Forschung und klinische Anwendung*. KVC-Verlag Essen 2024;6: 117-123:** In this study, the eight mistletoe preparations *Iscucin Abietis* (fir), *Crataegi* (hawthorn), *Mali* (apple tree), *Pini* (pine), *Populi* (poplar), *Salicis* (willow) and *Tiliae* (lime) were prepared according to the official pharmaceutical standards and tested for their mutagenic potential in a bacterial *in vitro* reverse mutation assay. None of the *Viscum album* L. preparations caused gene mutations and therefore, were all classified as non-mutagenic. These new data contribute to a more differentiated preclinical safety assessment of the tested aqueous mistletoe extracts from different host trees.

**Hsu HH, Lee AH, Tai SH: Viscolin-mediated antiapoptotic and neuroprotective effects in cortical neurons exposed to oxygen-glucose deprivation and rats subjected to transient focal cerebral ischemia. *Neurological Research* 2024;46,11:1063-1073. <https://doi.org/10.1080/01616412.2024.2381381>:** The aim of this study was to investigate the neuroprotective effects of Viscolin obtained from the extract of *Viscum colouratum*. Firstly, the cytotoxicity of Viscolin was analysed in primary neuronal cultures and its antioxidant and radical scavenging properties were determined. Subsequently, the optimal dose-response of viscolin in protecting against glutamate-induced neurotoxicity was identified and the therapeutic spectrum and potential of Viscolin to prevent necrotic and apoptotic damage in cultured neurons exposed to oxygen-glucose deprivation-induced neurotoxicity investigated. It was shown that Viscolin at a concentration of 10 µM could effectively reduce neuronal cell death up to 6 hours after glutamate-induced neurotoxicity. Also, the treatment significantly reduced DNA breakage, prevented the release of cytochrome c from the mitochondria into the cytosol, increased the expression of the anti-apoptotic protein Bcl-2 and reduced the expression of the pro-apoptotic protein Bax as well as the number of TUNEL-positive cells. In addition, the *in vivo* study in rats showed a reduction in brain infarction following middle cerebral artery occlusion.

## Clinic

### Efficacy/safety

**Felenda JE, Turek C, Stintzing FC: Safety, tolerability, therapeutic efficacy and quality of life (QoL) assessment of patients with malignant urogenital Tumors upon treatment with *Iscucin Populi* – results of a non-interventional study (NIS). In: Scheer R, Alban S, Beer AM et al. (Hrsg.): *Die Mistel in der Tumorthherapie 6 – Aktueller Stand der Forschung und klinische Anwendung*. KVC-Verlag Essen 2024;6:185-201:** In this non-interventional study (NIS), 69 patients with malignant urogenital tumours such as bladder and prostate cancer were treated with *Iscucin Populi* and its tolerability, use, course of therapy and quality of life were investigated. The preparation was prescribed in individual dosages for all degrees of severity in a curative, adjuvant or palliative setting, usually in addition to conventional therapy in accordance with medical guidelines. The global tolerability and efficacy were assessed as good to very good. The main side effects were fever and local reactions, which healed without any interference or subsequent damage. A stabilisation of the tumour state, partial remissions, decreases in tumour markers, an improvement or stabilisation of the general condition, general strengthening and increase in performance, psychological stabilisation and brightening of mood, decrease in sensitivity to cold and pain reduction were observed, and emotional and cognitive functions, sleep disorders, shortness of breath, diarrhoea and urinary symptoms also improved.

## Combination with oncological therapies

Schad F, Thronicke A, Hofheinz RD et al: Immune checkpoint blockade combined with abnoba VISCUM therapy is linked to improved survival in advanced or metastatic non-small-cell lung cancer patients: a registry study in accordance with the ESMO Guidance for Reporting Real-World Evidence. *Pharmaceuticals* 2024; 17:1713. <https://doi.org/10.3390/ph17121713>: In this real-world data study, survival was analysed in 300 patients with advanced or metastatic non-small cell lung cancer (NSCLC) who were included from the accredited Network Oncology registry in accordance with the ESMO-GROW criteria. 222 patients received immune checkpoint blockade (ICB) alone and 78 patients received ICB combined with mistletoe therapy (abnobaVISCUM). Patients in the combination group lived on median seven months longer (13.8 vs. 6.8 months). Furthermore, the risk of death in PD-L1-positive tumours was reduced by 75 per cent.

## Case reports

Haeck T, Simões-Wüst PA, Creutz v. Essen S: Mistletoe therapy in context of a multimodal treatment in a patient with severe cancer-survivorship fatigue-syndrome with comorbid sleep disorder: a case report. In: Scheer R, Alban S, Beer AM et al. (Hrsg.): *Die Mistel in der Tumortherapie 6 – Aktueller Stand der Forschung und klinische Anwendung*. KVC-Verlag Essen 2024;6: 216-226: This case report describes a female patient suffering from severe chronic tumour-associated fatigue (CRF), which was triggered by a *carcinoma in situ* of the vocal cords and the consecutive surgical and radiological therapies. The CRF was accompanied by cognitive fatigue and hypersomnia was aggravated by a post-traumatic-stress-disorder, anxiety and depression. To improve this complex dysregulation, the patient was treated over five years with a multimodal therapy (MT) consisting of subcutaneous (sc.) and intravenous (iv.) mistletoe therapy, CRF rehabilitation interventions (endurance and strength training, relaxation, mindfulness, nutrition and psychotherapy) and sleep therapy. The quality of sleep was clinically significantly improved by MT and fatigue was also sustainably reduced.

Park JB, Oh I, Chung S et al.: Clinical regression of chondrosarcoma applying high doses of *Viscum album* extracts (VAE) by intratumoral injection: a case report. In: Scheer R, Alban S, Beer AM et al. (Hrsg.): *Die Mistel in der Tumortherapie 6 – Aktueller Stand der Forschung und klinische Anwendung*. KVC-Verlag Essen 2024;6: 227-240: A 46-year-old male patient suffering from chondrosarcoma had two large-sized masses and a satellite tumour. The patient was treated intratumorally 24 times with abnobaVISCUM F (fraxini) 20 mg and also received 19 times Helixor A (abietis) 100 mg IV infusions weekly. 32 weeks after treatment the tumoral parenchyma showed a significant regression (> 70 % of the tumour size), the quality of life improved due to the reduction in tumour mass and symptoms such as shortness of breath, cough, haemoptysis and cachexia, and the survival time increased.

## Reviews

Adziakhmetova SL, Chervonnaya NM, Pozdnyakov DI, Popova OI: Component composition and features of biological activity of *Viscum album* (Viscaceae). *Doklady Biological Sciences* 2024; 518116–132. DOI: 10.1134/S0012496624701072: This review summarises data on the chemical composition and different characteristics of the biological activity of *Viscum album* L., the European mistletoe. Among secondary metabolites, viscotoxins, lectins, carbohydrates, amino acids, flavonoids, triterpene acids, and nitrogenous compounds predominate in *Viscum album*. Mistletoe extracts and their individual components exert various biological activities, including antitumour, immunomodulatory, and antidiabetic activities, and improve cognitive functions.

Scheer R: *Die Mistel in der Tumortherapie – eine Bestandsaufnahme (Mistletoe in tumour therapy – a review)*. *Zeitschrift für Phytotherapie* 2024;45: 267-274: Based on the role of mistletoe therapy in oncology, this review provides an overview of the mistletoe preparations available in Germany, the basic principles of their production and application, their effects and the results of clinical research, as the area of oncology in general has been undergoing major changes in the last few years and mistletoe therapy is also developing in this context.

**Yosri N, Kamal N, Mediani A, AbouZid S, Swillam A, Swilam M, Ayyat AM, Jantan I: Immunomodulatory activity and inhibitory effects of *Viscum album* on cancer cells, its safety profiles and recent nanotechnology development. *Planta Med* 2024. DOI: 10.1055/a-2412-8471:** This review article provides updated information from the past 10 years on the immunomodulatory activity and inhibitory effects of *Viscum album* on cancer cells, its safety profile, and recent nanotechnology development. It has been shown that *Viscum album* extracts and their bioactive phytochemicals, especially lectins, viscotoxins and polyphenols, improve immune function by promoting cytokine secretion and triggering both innate and adaptive immune responses, which can lead to improved immune defence against tumour cells.

### **Veterinärmedizin**

**Klingemann H: *Viscum album* (mistletoe) extract for dogs with cancer? *Front Vet Sci* 2024;10:1285354. DOI: 10.3389/fvets.2023.1285354:** This mini-review briefly summarises the experience of using *Viscum album* L. in humans in order to transfer it to canines with cancer. The mistletoe extract contains – among others – lectins and viscotoxins that have documented anti-proliferative effect on cancer cells as well as immunomodulatory function. Importantly, it also improves the well-being of patients with cancer due to its lectin ML-1 content, which can trigger the release of endorphins. Being cross-reactive with canine cells and having a relatively low side effect profile, mistletoe preparations might be considered as part of the treatment approach for dogs with cancer.

**Kumbaraci M, Kumbaraci BS, Basak Doganavsargil B et al.: Comparison of epoprostenol and *Viscum album* efficiencies in the treatment of avascular necrosis of the femoral head: An experimental animal study. *Histol Histopathol* 2024;39:1587-1595:** In this experimental study, the efficacy of epoprostenol and *Viscum album* in the treatment of avascular necrosis of the femoral head was compared in order to confirm the hypothesis that *Viscum album*, which has similar properties to epoprostenol on the vascular system, has the same effect. For this purpose, avascular necrosis was induced in the femoral heads of rabbits by surgical vascularisation and the rabbits were divided into 3 groups of 9 test animals each. Group 1 served as the control group, group 2 received an epoprostenol analogue (Ilomedin) and group 3 the *Viscum album* extract Helixor. It was found that *Viscum album* reduced the extent of necrosis and protected the articular cartilage, while epoprostenol increased repair and regeneration compared to the untreated group.