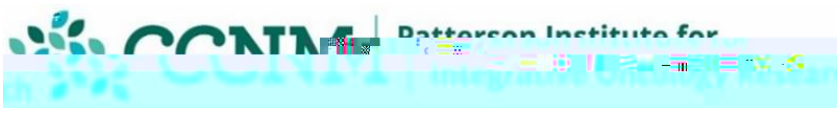
Healthcare Provider Resource

To view the patient version, visit [CCNM research]

Developed by:

The Patterson Institute for Integrative Oncology Research of the Canadian College of Naturopathic Medicine

Last updated: February 2024



General information

Proper name:
Viscum album Loranthaecea, *Viscum album L.*

Common names:
Mistletoe, European Mistletoe, Viscum album extracts (VAE)

Routes of administration:
Subcutaneous (SC), intravenous (IV), intramuscular, intrapleural, intratumoral, and intravesical instillation. This monograph will focus on the two most common routes: SC and IV.

Commercially available products:
Helixor®, Iscador®, abnobaVISCUM® (Isorel®, Lektinol®, Eurixor® are no longer available)

Common uses in cancer care:
Mistletoe extracts are commonly used to enhance immune function, support quality of life, reduce cancer-related side effects and symptoms, slow disease progression, reduce risk of recurrence, and improve survival.

Summary

Viscum album extracts (VAE) are used in integrative cancer care to support immune function, reduce side effects, improve quality of life (QOL), and possibly improve survival and recurrence. The most common routes of administration are subcutaneous (SC) injection and intravenous (IV) infusion; most research pertains to SC administration. Proposed mechanisms of action include immunomodulation of both innate and adaptive immune response, and direct cytotoxicity. Increased lymphocytes (T cells, B cells, and NK cells), dendritic cells, cytokines including INF-gamma and IL6, and presence of IgG antibodies to mistletoe lectins and viscotoxins have been observed. SC and IV VAE are

Methods

Monographs are created by the Patterson Institute for Integrative Oncology Research team and are updated approximately every two years. Comprehensive and structured literature searches were performed in Medline and Cochrane library from inception for English-language studies in people with cancer. The most recent search was completed on November 20, 2023. Additional scoping reviews were performed by research staff to obtain supporting information such as background information, mechanism of action, and safety data. Articles are duplicate-screened, data is extracted into standardized spreadsheets, and studies summarized.

Quality of Life

A randomized controlled study of patients with stage III and IV lung cancer receiving carboplatin-based chemotherapy found that VAE decreased the frequency of chemotherapy dose reductions (44% vs 13%, P = 0.005), grade 3-4 non-hematological toxicities (41% vs 16%, P = 0.043) and hospitalisations (54% vs 24%, P = 0.016).[32] No benefit was found for hematological toxicities (grade 3-4). An open label study of patients with metastatic treatment-resistant colorectal cancer initiating VAE reported that 40% of participants experienced symptomatic relief of nausea, vomiting, diarrhea, constipation, fatigue and dyspnea.[36] One RCT administering VAE during 5-DFUR to patients with early-stage gastric cancer reported a significantly lower rate of diarrhea in the intervention group compared to control (P = 0.014).[19]

Several specific symptoms have been improved with the use of VAE in clinical trials. Pain scores significantly improved in five studies (published in 6 reports) [17,18,20,34,39,41] and failed to improve in three,[49-51] all of which used the EORTC QLQ-C30 for QOL assessment. Appetite loss significantly improved in four studies. [17,18,20,41] Finally, insomnia and weight loss improved with the use of VAE compared to a control group in patients with advanced pancreatic cancer,[41] in this study weight increased by 5.3% in the VAE arm compared to a 3.2 % weight loss in the control arm.

Cancer-related fatigue (CRF) has been assessed in three clinical trials,[20,34,41] one observational study,[52] and two recent systematic reviews with meta-analysis.[55,56] The systematic reviews reported different findings. The first evaluated different modalities, either pharmacological or nonpharmacological, one of which was VAE. Three RCTs that used SC VAE injections were included.[55] There was no significant reduction of CRF with VAE injections. A random effects model treatment effect of −0.76 (−2.00, 0.48), P = 0.33 was calculated. The second systematic review and meta-analysis included 12 RCTs and 7 non-randomized studies, half of which included breast cancer patients.[56] The meta-analysis included 1494 participants from the 12 RCTs and 2668 from the 7 non-randomized trials. Heterogeneity between the studies was high, and most studies had a high risk of bias. A random-effects model revealed for RCTs, a standardized mean difference of – 0.48 (95% CI – 0.82 to – 0.14; P = 0.006), and for non-randomized trials, an odds ratio of 0.36 (95% CI 0.20 to 0.66; P = 0.0008). This was deemed to cause a moderate beneficial effect on CRF using VAE. One possible mechanism by which VAE may improve cancer-related fatigue is by attenuating markers of inflammation.[26]

The 2020 systematic review discussed previously[43] included a meta-analysis on QOL subdomains including specific symptoms across 10 studies. The standardized mean difference (SMD) of VAE compared to control in seven of 14 QOL dimensions were statistically significant in favor of mistletoe ($p < 0.05$). Although all symptoms improved with VAE, onl(e)9(d)y488(V)5(A)-4(y

VAE (Helixor and Eurixor)

stable disease) was 23.8%. The median QoL measured by Functional Assessment of Cancer Therapy scale was improved from 79.7 at week 1 to 93 at week 4, then slightly decreased to 89 at the end of treatment. The authors commented that IV VAE demonstrated manageable toxicities with disease control and improved QoL in a heavily pretreated solid tumor population.

The second phase 1 clinical study investigated escalating doses (200 mg to 2000 mg) of VAE in people with varied advanced cancers, but no concurrent cancer treatment. There were no serious AEs related to the IV VAE. The authors report that 2/21 patients had an unexpected positive clinical response observed by tumor marker changes and 1/21 had slowed progression.[64]

Mixed routes of administration

Five observational studies and one systematic review with meta-analysis combined data on patients administered VAE using different routes of administration, commonly SC, IV, and intratumoral. Of the observational studies, three included NSCLC patients, one included pancreatic cancer patients, and the fifth looked at patients with breast cancer.[67-71] The pancreatic and NSCLC studies used mistletoe (either SC, IV, intratumoral or combined) plus standard oncologic treatment, and found survival outcomes favoring the combined approach which were also cost-effective compared to standard oncologic treatment alone.[67,68] The second study among NSCLC patients yielded non-significant overall survival benefits, however, subgroup analysis revealed that patients with unresected tumours were more likely to benefit.[69] The third study was among lung cancer patients (mainly NSCLC), where 68% were stage III and IV.[71] Compared to patients who received no radiation or VAE, patients who received VAE had improvements in several EORTC scales including role functioning (P = 0.03), physical functioning (P = 0.02), cognitive functioning (P = 0.04), and social functioning (P = 0.04) at a 1-year follow-up. nother observational study in women with breast cancer was identified through our search, but due to methodological limitations it will not be discussed as it does not add meaningful information to our understanding of mistletoe.[70]

A systematic review and meta-analysis was conducted to evaluate the safety and efficacy of VAE, administered by various routes, during the oncological perioperative period. The study revealed preliminary but encouraging data for VAE usage, particularly in the context of the immune system in colorectal cancer; however, survival results were inconsistent. Seven RCTs (comprising 663 participants

required if reactions are severe.[84] The side effect rate for mistletoe injections based on systematic reviews has ranged from 17.5% to 21.5%, with the vast majority being expected local reactions.[46,84] More intense local skin reactions (> 5 cm diameter) occur in less than 1% of cases, [20] and are typically avoidable if a moderately progressive dosing approach is applied. One systematic review reported on treatment discontinuations due to adverse events from two RCTs. In these two studies, rates of discontinuation due to grade 3/4 toxicities ranged from 5-15%.[47]

Reported serious adverse events are rare. They include urticaria and angioedema,[37,44] hypotension and loss of consciousness,[85] anaphylaxis (< 1%),[23,85,86] and severe delayed type hypersensitivity reaction.[87]

Adverse reactions as reported in clinical trials and observational studies are reported below.

Common (> 5%): local injection-site reactions (e.g., swelling, erythema, pruritus, warmth, and induration).

Rare (< 5%): fatigue, fever, chills, headache, flu-like symptoms, diarrhea/flatulence, anorexia, depressive mood, and severe local reactions.

Rare but serious (1-4%): Angioedema, allergic reactions including anaphylaxis (<1%), hypotension and loss of consciousness, delayed hypersensitivity reaction, cellulitis at injection s

/F1 en-USoneW* nBT/F1 11.56ETOqET.043370912370rggET.043370912370R 1 42IoeW- 11n- 1oin.48f(eu) o

outcomes or toxicity. A study in 2017 found no induction or major inhibition of nine major cytochrome P450 isoenzymes with Helixor VAE products, making a clinically relevant pharmacokinetic herb-drug interaction unlikely.[90]

Although direct pharmacokinetic and pharmacodynamic studies evaluating interactions are lacking, the totality of evidence supports the premise that it is unlikely that there is any negative interaction with combined use with cytotoxic chemotherapy.

There is no known interaction of VAE with radiation therapy. Some studies in table 1 and 2 included people receiving radiation therapy without any negative interactions noted.

Immunotherapy and targeted therapies

Due to the immunomodulatory properties of VAE, there has been some concern about the safety of combined use of VAE and immunotherapies and targeted therapies due to a theoretical additive effect. However, available evidence thus far has not demonstrated an increase in toxicity, and in fact has generally reported lower rates of adverse effects with combined use.[91-96]

Several observational studies assessed the safety of VAE (IV or SC) alongside targeted therapies including monoclonal antibodies (mAB), immune checkpoint inhibitors (ICIs), CDK 4/6 inhibitors (CDKi), and tyrosine kinase inhibitors (TKIs). The first included 242 patients with breast and gynecological cancer receiving targeted therapies with or without Helixor primarily administered SC.[96] Targeted therapies included mAB (79.8%), CDKi (10.7%), and ICIs (5.4%). Add-on VAE did not negatively alter targeted therapies' safety profile (χ 2 = 0.107, P = 0.99). No adverse events were reported, and a trend toward improved adherence to targeted therapy usage was observed in the combination group. The second study included 310 patients receiving a variety of mAbs, ICIs, and TKIs (primarily bevacizumab, rituximab, trastuzumab, or erlotinib).[93] There was a significantly lower AE rate in the combined group compared to control (20.1% vs 30.2%, P = 0.04) and a lower rate of discontinuation of standard oncology treatment in the combined vs control group (35% vs 60.5%, P = 0.03). Thirdly, a small pilot study evaluated

results.[97] As noted below, when immunosuppressive treatments are applied, mistletoe use should be avoided.

Interactions with other medications:

Warfarin:

A case report describing a possible interaction between warfarin and VAE was published.[98] The patient was treated with warfarin for atrial fibrillation, and upon initiating nab-paclitaxel and gemcitabine chemotherapy he experienced melena and an INR of 7.3. The patient revealed that he used SC injections of VAE. The authors hypothesized that VAE may inhibit cytochrome P450 (CYP) isoforms;1A2, 2C9, and 3A4, which metabolize warfarin. Additionally, nab-paclitaxel may interact with warfarin and thus the combination of both may have been involved. However, other research has indicated that VAE is not an inhibitor or inducer of major CYP P450 isoforms,[99] thus what contribution VAE made in this scenario is unclear.

Cautions and Contraindications

Mistletoe should not be used by anyone with a known allergy or hypersensitivity to mistletoe. There is insufficient evidence regarding the safety of mistletoe during pregnancy and lactation. Mistletoe should be used cautiously in people with autoimmune (AI) conditions although this is not a contraindication. Use should be avoided if immune suppressant medication is required to manage the AI condition due to the immune-stimulating properties of mistletoe.[2,9,13,100] Given the need for immune suppression, mistletoe should not be used following a recent organ or bone marrow transplant. Mistletoe should be used cautiously in patients with brain tumors or metastases if there is unmanaged cerebral edema due to possible peri-tumoral inflammation with VAE, although evidence of harm from clinical studies is lacl3ireW* nBT/99(l)-4(i)-4(ni)-4(c)9(a)9(nBT/99(l)-4(i)-4(ni)-4(c)9(a)9(nBT/99(l)-4(i)-4(ni)-4(c)9(a)9

Table 1: Clinical trials of subcutaneous (SC) mistletoe for cancer

			3X/ week during 6 cycles of chemotherapy. Stopped within 3 weeks of chemo discontinuation

Troger et al (2013)[33]	Phase III Randomized Controlled Open-Label	**N:** 220 **Ca Type:** Pancreatic Cancer **Stage:** III (n= 121) IV (n= 99) **ECOG** 1 (n=112) 2-4 (n=108) **Prior Tx:** 205 had surgery	**Agent:** Iscador Q **Dose:** escalating dose (0.01 mg - 10 mg)

Semiglazov et al (2006)[42]	Randomized Placebo Controlled Double-Blind	**N:** 352 **Ca Type:** Breast, stage II/III	**Agent:** Lektinol **(**PS76A2, an aqueous mistletoe extract) **Dose:** 15 ng mistletoe lectin/0.5 ml **Route:** SC **Admin:** 2x/week for 4-6 cycles of chemotherapy **Comparison:**

Oei et al (2020) [70]	Retrospective	**N**: 319 **Ca type**: Breast cancer **Stage**: Non-metastatic	**Agent:** AbnobaViscum, Helixor, Iscador, and Iscucin **Dose:** Not reported **Route:** SC and IV **Administration:** Either alone or with chemotherapy. Duration ≥ 4 weeks **Comparison**: Chemotherapy alone, mistletoe alone, combined therapy, or no mistletoe or chemotherapy (control – this group could receive endocrine therapy/immunotherapy)	All patients offered standard oncology therapies	Internal coherence (marker of resilience, optimism, sense of control) (ICS questionnaire) Cancer-related fatigue (EORTC QLQ C30) QOL (EORTC QLQ C30)	**i)** Patients receiving VAE but no chemotherapy experienced significant beneficial effects on thermo-coherence ($p < 0.05$), affective fatigue ($p < 0.05$), and seven EORTC subscales at 24 months (all $p < 0.05$). Note these changes are within-group, not between group comparisons. **ii)** Chemo-, immuno- and endocrine therapies had a 17-, 17- and 6-point decline, respectively, for EORTC fatigue ($P = 0.0004$), whereas the VAE group improved 12 points. **iii)** VAE group improved in insomnia and physical functioning scores while these scores worsened in conventional care groups ($p = 0.009$ and $p = 0.005$, respectively). **iv)** Caution is advised when reviewing these results given the possibility of selective reporting and questionable statistical analysis. Additionally, note that most positive results were for the VAE-only group not VAE + chemotherapy.
Thronicke et al (2020) [69]	Retrospective	**N**: 275 **Ca type**: NSCLC patients **Stage**: I -IIIA	**Agent:** Abnobaviscum, Helixor, and Iscador **Dose:** **Route:** SC route or by off-label **IV administ** [illegible] patients) **Administration:** 95 reW* nBT/F1			

Thronicke et al (2018)[93]	Retrospective	**N**: 310 **Ca type**: Multiple types **Stage**: 0-IV	**Agent:** Fraxini, Quercus, Mali **Dose:** Not reported **Route:** SC **Administration:** Median duration was 3.8 months (114 days) **Comparison**: Targeted therapy alone	Targeted therapy	Safety with targeted therapy	**i)** Mistletoe + targeted therapy, compared to targeted therapy

			Comparison: chemotherapy only and VA only			
Steele et al (2015) [117]	Retrospective	**N:** 123 **Ca Type:** multiple types **Stage:** mixed and some unknown, but 47.2% stage IV	**Agent**: Helixor, Abnoba, Iscucin **Dose:** 0.02 to 250mg, median dose 60mg **Route**: intratumoral **Administration:** varied, majority received 2-6 applications, up to 1 month **Comparison:** NA	Mixed (SC, IV, both)	Safety: AE's & ADRs	**i)** 26 patients experienced a total of 74 ADRs (21.1%). **ii)** Most common ADRs were body temperature increase or immune related effect, of which 83.8% were mild and 14.9% moderate. **iii)** One possible severe ADR occurred (hypertension) with no serious ADRs occurring. **iv)** Intratumoral ADR rates were 3x higher than SC and 5x higher than intravenous application rates when compared with external data.
Sunjic et al (2015) [103]	Retrospective Case-report series	**N:** 74 **Ca Type:** multiple Types **Stage**: majority were advanced stages	**Agent**: Isorel (A, M & P) **Dose:** not reported, as per manufacturers guidelines **Route:** SC, IM, IV **Administration:** 3X/week first year after diagnosis, then maintained or reduced to 1X/week in cases of remission **Comparison:** NA	Conventional care (primarily surgery and radiation)	Clinical Effect (not adequately described)	**i)** There was no tumor recurrence in 47% of cases, partial cancer regression in 38% of cases, and no cases of worsening condition. **ii)** Not much can be stated from this study due to poor methodology.
Von Schoen-Angerer (2015) [104]	Retrospective Case-series	**N:** 8 **Ca Type:** Bladder Cancer **Stage**: Majority were non-muscle invasive cancer.	**Agent**: Iscucin Salicis **Route**: SC **Dose:** strengths F (0.125mg), G (2.5mg) and H (50mg) **Administration:** varied from 1x/week to daily based on fever and inflammatory reactions **Comparison: NA**	Mixed	Recurrence	**i)** Median tumor-free duration was 48.5 months. **ii)** High dose mistletoe showed possible benefit in 5 of 8 patients, 2 patients could not be assessed and 1 showed uncertain effects of mistletoe. **iii)** No tumor progression was observed in any of the 8 patients. **iv)** No patient stopped treatment due to intolerance/side-effects.
Bock et al (2014) [52]	Retrospective	**N:** 324 **Ca Type:** Colorectal **Stage:** non-metastasized CRC, stages I-III	**Agent**: Iscador Q **Dose:** total 16 to 20mg per week **Route:** SC **Administration:** daily doses were left up to physician's discretion **Comparison:** NA	Chemotherapy or radio-chemotherapy	Cancer Related Fatigue	**i)** Those who received mistletoe in addition to standard care hnopy c

Steele et al (2014) [82]	Retrospective	**N:** 475 **Ca Type:** multiple types **Stages:** I-IV	**Agent**: Helixor, Abnoba, Iscador **Dose:** ranged 10 to 400mg **Route**: IV and SC **Administration:** mixed **Comparison:** NA	Conventional care	Safety: AE's & ADRs	**i)** No serious ADRs occurred. **ii)** 22 patients reported 32 ADRs (59.4% mild, 40.6% moderate). **iii)** Iscador brand showed relative higher frequency of ADRs compared to the other products. **iv)** Intravenous mistletoe had significantly less ADRs than subcutaneous administration (4.6% vs 8.4%, P = 0.005).
Steele et al (2014) [83]	Observational	**N:** 1923 **Ca Type:** multiple types **Stage:** 0-IV	**Agent**: mixed **Dose:** varied, ≤0.02 to 60mg **Route:** SC **Administration:** varied, most often 3X/week, median length of mistletoe therapy 4.6 months **Comparison:**			

References

1. Horneber MA, Bueschel G, Huber R, Linde K, Rostock M. Mistletoe therapy in oncology. *The Cochrane database of systematic reviews*

17. Troger W, Zdrale Z, Tisma N, Matijasevic M. Additional Therapy with a Mistletoe Product during Adjuvant Chemotherapy of Breast Cancer Patients Improves Quality of Life: An Open Randomized Clinical Pilot Trial. *Evid Based Complement Alternat Med*. 2014;2014:430518. doi:10.1155/2014/430518
18. Pelzer F, Troger W, Nat DR. Complementary Treatment with Mistletoe Extracts During Chemotherapy: Safety, Neutropenia, Fever, and Quality of Life Assessed in a Randomized Study. *Journal of alternative and complementary medicine (New York, NY)*. Sep/Oct 2018;24(9-10):954-

34.

71.

88. Schlappi M, Ewald C, Kuehn JJ, Weinert T, Huber R. Fever Therapy With Intravenously Applied Mistletoe Extracts for Cancer Patients: A Retrospective Study. *Integrative cancer therapies*. Dec 2017;16(4):479-484. doi:10.1177/1534735416658121
89. Irct20080901001165N. Determining the efficacy of Iscador in cancer.
90. Schink M, Dehus O. Effects of mistletoe products on pharmacokinetic drug turnover by inhibition and induction of cytochrome P450 activities. *BMC complementary and alternative medicine*. Dec 4 2017;17(1):521. doi:10.1186/s12906-017-2028-1
91.

107. Galun D, Bogdanovic A, Zivanovic M, Troger W. Overall survival after transcatheter hepatic mistletoe therapy of patients with hepatocellular carcinoma. Journal: Conference Abstract. *Phytomedicine : international journal of phytotherapy and phytopharmacology*. 2019;61:6-. doi:10.1016/j.phymed.2019.09.128
108. Lee YG, Jung I, Koo DH, et al. Efficacy and safety of Viscum album extract (Helixor-M) to treat malignant pleural effusion in patients with lung cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. Sep 14 2018;doi:10.1007/s00520-018-4455-z
109. Rose A, El-Leithy T, vom Dorp F, et al. Mistletoe Plant Extract in Patients with Nonmuscle Invasive Bladder Cancer: Results of a Phase Ib/IIa Single Group Dose Escalation Study. *The Journal of urology*. 2015;194(4):939-43. doi:10.1016/j.juro.2015.04.073
110. Gaafar R, Abdel Rahman AR, Aboulkasem F, El Bastawisy A. Mistletoe preparation (ignantn/0.00000912 (t)-on/0.00000