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Mistletoe Extracts (PDQ®)–Health Professional Version

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Overview

This cancer information summary provides an overview of the use of mistletoe as a treatment for people with cancer. The summary includes a brief history of mistletoe research, the results of clinical trials, and possible side effects of mistletoe use.

This summary contains the following key information:

- Mistletoe is a semiparasitic plant that has been used for centuries to treat numerous human ailments.
- Mistletoe is used commonly in Europe, where a variety of different extracts are manufactured and marketed as injectable prescription drugs. These injectable drugs are not available commercially in the United States and are not approved as a treatment for people with cancer.
- Mistletoe is one of the most widely studied CAM therapies for cancer. In certain European countries, the preparations made from European mistletoe (*Viscum album*, Loranthaceae) are among the most prescribed drugs offered to cancer patients.
- Although mistletoe plants and berries are considered poisonous to humans, few serious side effects have been associated with mistletoe extract use.
- The use of mistletoe as a treatment for people with cancer has been investigated in clinical studies. Reports of improved survival and/or quality of life have been common, but many of the studies had major weaknesses that raise doubts about the reliability of the findings.
- At present, the use of mistletoe cannot be recommended outside the context of well-designed clinical trials. Such trials will be valuable to determine more clearly whether mistletoe can be useful in the treatment of specific subsets of cancer patients.

Many of the medical and scientific terms used in this summary are hypertext linked (at first use in each section) to the NCI Dictionary of Cancer Terms, which is oriented toward nonexperts. When a linked term is clicked, a definition will appear in a separate window.

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General Information

Mistletoe, a semiparasitic plant, holds interest as a potential anticancer agent because extracts derived from it have been shown to kill cancer cells *in vitro* [1-10] to down-regulate central genes involved in tumor progression, malignancy, and cell migration and invasion, such as TGF-β and matrix-metalloproteinases. [11,12] Mistletoe extracts have been shown to do the following:[10-31]

- Enforce natural killer cell-mediated tumor cell lysis.
- Reduce the migratory and invasive potential of tumor cells.
- Stimulate immune system cells both *in vitro* and *in vivo*.

Three components of mistletoe, namely viscotoxins, polysaccharides, and lectins, may be responsible for these effects.[10,13-15,19-21,23-25,32-39] Viscotoxins are small proteins that exhibit cell-killing activity and possible immune system–stimulating activity.[1,6,20,21,40,41] Lectins are complex molecules made of both protein and carbohydrates that are capable of binding to the outside of cells (e.g., immune system cells) and inducing biochemical changes in them.[10,42-45]

In view of mistletoe's ability to stimulate the immune system, it has been classified as a type of biological response modifier.[42] Biological response modifiers constitute a diverse group of biological molecules that have been used individually, or in combination with other agents, to treat cancer or to lessen the side effects of anticancer drugs. Mistletoe extracts have been demonstrated in preclinical settings to have other mechanisms of action, such as antiangiogenesis.[29]

Preparations from mistletoe extracts are most frequently used in the treatment of cancer patients in German-speaking countries.[46] Commercially available extracts are marketed under a variety of brand names, including Iscador (see explanation of suffixes below), Eurixor, Helixor, Isorel, Iscucin, Plenosol, and abnobaVISCUM. Some extracts are marketed under more than one name. Iscador, Isorel, and Plenosol are also sold as Iscar, Vysorel, and Lektinol, respectively. All of these products are prepared from *Viscum album* (Loranthaceae) (*Viscum album* L. or European mistletoe). They are not sold as a drug in the United States. Eurixor, Isorel, and Vysorel are no longer available on the market for sale.

In addition to European mistletoe, extracts from a type of Korean mistletoe (*Viscum album* var. *coloratum* [Kom.] Ohwi) have demonstrated *in vitro* and *in vivo* cytotoxicity in laboratory studies.[47-51]

Mistletoe grows on several types of trees, and the chemical composition of extracts derived from it depends on the following:[8,43,52-55]

- Species of the host tree (e.g., apple, elm, oak, pine, poplar, and spruce).
- Time of year harvested.
- How the extracts are prepared.
- The commercial producer.

Mistletoe extracts are prepared as aqueous solutions or solutions of water and alcohol, and they can be fermented or unfermented.[4,6,22,52,53,56-59] Some extracts are prepared according to homeopathic principles, and others are not. Accordingly, as homeopathic preparations, they are typically not chemically

standardized extracts.[10,60] In addition, the commercial products can be subdivided according to the species of host tree, which is typically indicated in the product name by a suffix letter. Iscador, a fermented aqueous extract of *Viscum album* L. that is prepared as a homeopathic drug, is marketed as one of the following:[57]

- IscadorM (from apple trees; *Malus domestica*).
- IscadorP (from pine trees; *Pinus sylvestris*).
- IscadorQu (from oak trees; *Quercus robur*).
- IscadorU (from elm trees; *Ulmus minor*).

Helixor, an unfermented aqueous extract of *Viscum album* L. that is standardized by its biological effect on human leukemia cells *in vitro*, is marketed as one of the following:[57]

- HelixorA (from spruce trees; *Picea abies*).
- HelixorM (from apple trees).
- HelixorP (from pine trees; *Pinus sylvestris*).

Eurixor (which is no longer available on the market for sale), an unfermented aqueous extract of *Viscum album* L. harvested from poplar trees, is reportedly standardized to contain a specific amount of one of mistletoe's lectins (i.e., the lectin ML-1; refer to the History section of this summary for more information).[57] Some proponents contend the choice of extract should depend on the type of tumor and the gender of the patient.[55,57,61,62]

A recombinant ML-1 from *Escherichia coli* bacteria known as rViscumin or aviscumine has been studied in the laboratory and in phase I clinical trials. Because this is not an extract of mistletoe, it is out of the purview of this summary.[63]

Mistletoe extracts are usually given by subcutaneous injection, although administration by other routes (i.e., oral, intrapleural, intratumoral, and intravenous) has been described.[19,22-26,39,43,55,57,60,64-70] In most reported studies, subcutaneous injections were given 2 to 3 times a week, but the overall duration of treatment varied considerably.

Viscum album is listed in the Homeopathic Pharmacopoeia of the United States, which is the officially recognized compendium for homeopathic drugs in this country.[71] Although the U.S. Food and Drug Administration (FDA) has regulatory authority over homeopathic drugs, this authority is usually not exercised unless the drugs are formulated for injection or there is evidence of severe toxicity.

Before researchers can conduct clinical drug research in the United States, they must file an Investigational New Drug (IND) application with the FDA. IND approval is also required for clinical investigation of homeopathic drugs. The FDA does not disclose information about IND applications or approvals; this information can be released only by the applicants. At least two U.S. investigators were given IND approval to study mistletoe as a treatment for people with cancer (NCCAM-02-AT-260 and TJUH-01F.45).

In this summary, the mistletoe extract or product used in each study will be specified wherever possible.

References

1. Jung ML, Baudino S, Ribéreau-Gayon G, et al.: Characterization of cytotoxic proteins from mistletoe (Viscum album L.). Cancer Lett 51 (2): 103-8, 1990. [PUBMED Abstract]
2. Kuttan G, Vasudevan DM, Kuttan R: Effect of a preparation from Viscum album on tumor development in vitro and in mice. J Ethnopharmacol 29 (1): 35-41, 1990. [PUBMED Abstract]
3. Walzel H, Jonas L, Rosin T, et al.: Relationship between internalization kinetics and cytotoxicity of mistletoe lectin I to L1210 leukaemia cells. Folia Biol (Praha) 36 (3-4): 181-8, 1990. [PUBMED Abstract]
4. Janssen O, Scheffler A, Kabelitz D: In vitro effects of mistletoe extracts and mistletoe lectins. Cytotoxicity towards tumor cells due to the induction of programmed cell death (apoptosis). Arzneimittelforschung 43 (11): 1221-7, 1993. [PUBMED Abstract]
5. Jurin M, Zarković N, Hrzenjak M, et al.: Antitumorous and immunomodulatory effects of the Viscum album L. preparation Isorel. Oncology 50 (6): 393-8, 1993 Nov-Dec. [PUBMED Abstract]
6. Schaller G, Urech K, Giannattasio M: Cytotoxicity of different viscotoxins and extracts from the European subspecies Viscum album L. Phytother Res 10 (6): 473-7, 1996.
7. Gabius HJ, Darro F, Remmelink M, et al.: Evidence for stimulation of tumor proliferation in cell lines and histotypic cultures by clinically relevant low doses of the galactoside-binding mistletoe lectin, a component of proprietary extracts. Cancer Invest 19 (2): 114-26, 2001. [PUBMED Abstract]
8. Maier G, Fiebig HH: Absence of tumor growth stimulation in a panel of 16 human tumor cell lines by mistletoe extracts in vitro. Anticancer Drugs 13 (4): 373-9, 2002. [PUBMED Abstract]
9. Franz H: Mistletoe lectins and their A and B chains. Oncology 43 (Suppl 1): 23-34, 1986. [PUBMED Abstract]
10. Mengs U, Göthel D, Leng-Peschlow E: Mistletoe extracts standardized to mistletoe lectins in oncology: review on current status of preclinical research. Anticancer Res 22 (3): 1399-407, 2002 May-Jun. [PUBMED Abstract]
11. Podlech O, Harter PN, Mittelbronn M, et al.: Fermented mistletoe extract as a multimodal antitumoral agent in gliomas. Evid Based Complement Alternat Med 2012: 501796, 2012. [PUBMED Abstract]
12. Schötterl S, Hübner M, Armento A, et al.: Viscumins functionally modulate cell motility-associated gene expression. Int J Oncol 50 (2): 684-696, 2017. [PUBMED Abstract]
13. Hostanska K, Hajto T, Spagnoli GC, et al.: A plant lectin derived from Viscum album induces cytokine gene expression and protein production in cultures of human peripheral blood mononuclear cells. Nat Immun 14 (5-6): 295-304, 1995. [PUBMED Abstract]
14. Beuth J, Stoffel B, Ko HL, et al.: Immunomodulating ability of galactoside-specific lectin standardized and depleted mistletoe extract. Arzneimittelforschung 45 (11): 1240-2, 1995. [PUBMED Abstract]
15. Lenartz D, Stoffel B, Menzel J, et al.: Immunoprotective activity of the galactoside-specific lectin from mistletoe after tumor destructive therapy in glioma patients. Anticancer Res 16 (6B): 3799-802, 1996 Nov-Dec. [PUBMED Abstract]
16. Fischer S, Scheffler A, Kabelitz D: Oligoclonal in vitro response of CD4 T cells to vesicles of mistletoe extracts in mistletoe-treated cancer patients. Cancer Immunol Immunother 44 (3): 150-6, 1997. [PUBMED Abstract]
17. Preisfeld A: Influence of aqueous mistletoe preparations on humoral immune parameters with

emphasis on the cytotoxicity of human complement in breast cancer patients. Forsch Komplementarmed 4 (4): 224-8, 1997.

18. Chernyshov VP, Omelchenko LI, Heusser P, et al.: Immunomodulatory actions of Viscum album (Iscador) in children with recurrent respiratory disease as a result of the Chernobyl nuclear accident. Complement Ther Med 5 (3): 141-6, 1997.

19. Heiny BM, Albrecht V, Beuth J: Correlation of immune cell activities and beta-endorphin release in breast carcinoma patients treated with galactose-specific lectin standardized mistletoe extract. Anticancer Res 18 (1B): 583-6, 1998 Jan-Feb. [PUBMED Abstract]

20. Stein GM, Schaller G, Pfüller U, et al.: Characterisation of granulocyte stimulation by thionins from European mistletoe and from wheat. Biochim Biophys Acta 1426 (1): 80-90, 1999. [PUBMED Abstract]

21. Stein GM, Schaller G, Pfüller U, et al.: Thionins from Viscum album L: influence of the viscotoxins on the activation of granulocytes. Anticancer Res 19 (2A): 1037-42, 1999 Mar-Apr. [PUBMED Abstract]

22. Mistletoe. In: Murray MT: The Healing Power of Herbs. Prima Publishing, 1995, pp 253-9.

23. Lenartz D, Dott U, Menzel J, et al.: Survival of glioma patients after complementary treatment with galactoside-specific lectin from mistletoe. Anticancer Res 20 (3B): 2073-6, 2000 May-Jun. [PUBMED Abstract]

24. Steuer-Vogt MK, Bonkowsky V, Ambrosch P, et al.: The effect of an adjuvant mistletoe treatment programme in resected head and neck cancer patients: a randomised controlled clinical trial. Eur J Cancer 37 (1): 23-31, 2001. [PUBMED Abstract]

25. Goebell PJ, Otto T, Suhr J, et al.: Evaluation of an unconventional treatment modality with mistletoe lectin to prevent recurrence of superficial bladder cancer: a randomized phase II trial. J Urol 168 (1): 72-5, 2002. [PUBMED Abstract]

26. Stauder H, Kreuser ED: Mistletoe extracts standardised in terms of mistletoe lectins (ML I) in oncology: current state of clinical research. Onkologie 25 (4): 374-80, 2002. [PUBMED Abstract]

27. Saha C, Das M, Stephen-Victor E, et al.: Differential Effects of Viscum album Preparations on the Maturation and Activation of Human Dendritic Cells and $CD4^+$ T Cell Responses. Molecules 21 (7): , 2016. [PUBMED Abstract]

28. Hegde P, Maddur MS, Friboulet A, et al.: Viscum album exerts anti-inflammatory effect by selectively inhibiting cytokine-induced expression of cyclooxygenase-2. PLoS One 6 (10): e26312, 2011. [PUBMED Abstract]

29. Elluru SR, VAN Huyen JP, Delignat S, et al.: Antiangiogenic properties of viscum album extracts are associated with endothelial cytotoxicity. Anticancer Res 29 (8): 2945-50, 2009. [PUBMED Abstract]

30. Elluru SR, Duong van Huyen JP, Delignat S, et al.: Induction of maturation and activation of human dendritic cells: a mechanism underlying the beneficial effect of Viscum album as complimentary therapy in cancer. BMC Cancer 8: 161, 2008. [PUBMED Abstract]

31. Elluru S, Duong Van Huyen JP, Delignat S, et al.: Molecular mechanisms underlying the immunomodulatory effects of mistletoe (Viscum album L.) extracts Iscador. Arzneimittelforschung 56 (6A): 461-6, 2006. [PUBMED Abstract]

32. Frohne D, Pfander HJ: Viscum album. In: Frohne D, Pfander HJ: Giftpflanzen: ein Handbuch für Apotheker, Ärzte, Toxikologen und Biologen. 3rd rev. ed. Wissenschaftliche Verlagsgesellschaft, 1987,

pp 179-80.

33. Pusztai A, Grant G, Pfuller U, et al.: Nutritional and metabolic effects of mistletoe lectin ML-1 (type 2 RIP) in the rat. In: European Cooperation in the Field of Scientific and Technical Research: COST 98: Effects of Antinutrients on the Nutritional Value of Legume Diets. European Commission, Directorate-General XII, Science, Research and Development, 1998, pp 164-7.

34. Pusztai A, Grant G, Gelencsér E, et al.: Effects of an orally administered mistletoe (type-2 RIP) lectin on growth, body composition, small intestinal structure, and insulin levels in young rats. J Nutr Biochem 9 (1): 31-6, 1998.

35. Ewen SWB, Bardocz S, Grant G, et al.: The effects of PHA and mistletoe lectin binding to epithelium of rat and mouse gut. In: European Cooperation in the Field of Scientific and Technical Research: COST 98: Effects of Antinutrients on the Nutritional Value of Legume Diets. European Commission, Directorate-General XII, Science, Research and Development, 1998, pp 221-5.

36. Pryme IF, Bardocz S, Grant G, et al.: The plant lectins PHA and ML-1 suppress the growth of a lymphosarcoma tumour in mice. In: European Cooperation in the Field of Scientific and Technical Research: COST 98: Effects of Antinutrients on the Nutritional Value of Legume Diets. European Commission, Directorate-General XII, Science, Research and Development, 1998, pp 215-20.

37. Tubeuf KFv, Neckel G, Marzell H: Monographie der Mistel. R. Oldenbourg, 1923.

38. Teuscher E: Viscum album. In: Hansel R, Keller K, Rimpler H, et al.: Hagers Handbuch der Pharmazeutischen Praxis, Vol. 6. 5th ed. Springer-Verlag, 1994, pp 1160-83.

39. Grossarth-Maticek R, Kiene H, Baumgartner SM, et al.: Use of Iscador, an extract of European mistletoe (Viscum album), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. Altern Ther Health Med 7 (3): 57-66, 68-72, 74-6 passim, 2001 May-Jun. [PUBMED Abstract]

40. Capernaros Z: The golden bough: the case for mistletoe. Eur J Herbal Med 1 (1):19-24, 1994.

41. Schrader G, Apel K: Isolation and characterization of cDNAs encoding viscotoxins of mistletoe (Viscum album). Eur J Biochem 198 (3): 549-53, 1991. [PUBMED Abstract]

42. Gabius HJ, Gabius S, Joshi SS, et al.: From ill-defined extracts to the immunomodulatory lectin: will there be a reason for oncological application of mistletoe? Planta Med 60 (1): 2-7, 1994. [PUBMED Abstract]

43. Samtleben R, Hajto T, Hostanska K, et al.: Mistletoe lectins as immunostimulants (chemistry, pharmacology and clinic). In: Wagner H, ed.: Immunomodulatory Agents from Plants. Birkhauser Verlag, 1999, pp 223-41.

44. Abdullaev FI, de Mejia EG: Antitumor effect of plant lectins. Nat Toxins 5 (4): 157-63, 1997. [PUBMED Abstract]

45. Kilpatrick DC: Mechanisms and assessment of lectin-mediated mitogenesis. Mol Biotechnol 11 (1): 55-65, 1999. [PUBMED Abstract]

46. Horneber MA, Bueschel G, Huber R, et al.: Mistletoe therapy in oncology. Cochrane Database Syst Rev (2): CD003297, 2008. [PUBMED Abstract]

47. Khil LY, Kim W, Lyu S, et al.: Mechanisms involved in Korean mistletoe lectin-induced apoptosis of cancer cells. World J Gastroenterol 13 (20): 2811-8, 2007. [PUBMED Abstract]

48. Kim MS, Lee J, Lee KM, et al.: Involvement of hydrogen peroxide in mistletoe lectin-II-induced apoptosis

of myeloleukemic U937 cells. Life Sci 73 (10): 1231-43, 2003. [PUBMED Abstract]

49. Choi SH, Lyu SY, Park WB: Mistletoe lectin induces apoptosis and telomerase inhibition in human A253 cancer cells through dephosphorylation of Akt. Arch Pharm Res 27 (1): 68-76, 2004. [PUBMED Abstract]
50. Romagnoli S, Fogolari F, Catalano M, et al.: NMR solution structure of viscotoxin C1 from Viscum album species Coloratum ohwi: toward a structure-function analysis of viscotoxins. Biochemistry 42 (43): 12503-10, 2003. [PUBMED Abstract]
51. Yoon TJ, Yoo YC, Kang TB, et al.: Antitumor activity of the Korean mistletoe lectin is attributed to activation of macrophages and NK cells. Arch Pharm Res 26 (10): 861-7, 2003. [PUBMED Abstract]
52. Ribéreau-Gayon G, Jung ML, Di Scala D, et al.: Comparison of the effects of fermented and unfermented mistletoe preparations on cultured tumor cells. Oncology 43 (Suppl 1): 35-41, 1986. [PUBMED Abstract]
53. Jäggy C, Musielski H, Urech K, et al.: Quantitative determination of lectins in mistletoe preparations. Arzneimittelforschung 45 (8): 905-9, 1995. [PUBMED Abstract]
54. Zee-Cheng RK: Anticancer research on Loranthaceae plants. Drugs Future 22 (5): 519-30, 1997.
55. Kaegi E: Unconventional therapies for cancer: 3. Iscador. Task Force on Alternative Therapies of the Canadian Breast Cancer Research Initiative. CMAJ 158 (9): 1157-9, 1998. [PUBMED Abstract]
56. Stein G, Berg PA: Non-lectin component in a fermented extract from Viscum album L. grown on pines induces proliferation of lymphocytes from healthy and allergic individuals in vitro. Eur J Clin Pharmacol 47 (1): 33-8, 1994. [PUBMED Abstract]
57. Kleijnen J, Knipschild P: Mistletoe treatment for cancer: review of controlled trials in humans. Phytomedicine 1: 255-60, 1994.
58. Wagner H, Jordan E, Feil B: Studies on the standardization of mistletoe preparations. Oncology 43 (Suppl 1): 16-22, 1986. [PUBMED Abstract]
59. Zarkovic N, Vukovic T, Loncaric I, et al.: An overview on anticancer activities of the Viscum album extract Isorel. Cancer Biother Radiopharm 16 (1): 55-62, 2001. [PUBMED Abstract]
60. Mellor D: Mistletoe in homoeopathic cancer treatment. Prof Nurse 4 (12): 605-7, 1989. [PUBMED Abstract]
61. Fellmer KE: A clinical trial of Iscador: follow-up treatment of irradiated genital carcinomata for the prevention of recurrences. Br Homeopath J 57: 43-7, 1968.
62. Kjaer M: Mistletoe (Iscador) therapy in stage IV renal adenocarcinoma. A phase II study in patients with measurable lung metastases. Acta Oncol 28 (4): 489-94, 1989. [PUBMED Abstract]
63. Schöffski P, Riggert S, Fumoleau P, et al.: Phase I trial of intravenous aviscumine (rViscumin) in patients with solid tumors: a study of the European Organization for Research and Treatment of Cancer New Drug Development Group. Ann Oncol 15 (12): 1816-24, 2004. [PUBMED Abstract]
64. Matthes HF, Schad F, Buchwald D, et al.: Endoscopic ultrasound-guided fine-needle Injection of Viscum album L. (mistletoe; Helixor M) in the therapy of primary inoperable pancreas cancer: a pilot study. [Abstract] Gastroenterology 128 (Suppl 2): A-T988, A433-A434, 2005.
65. Matthes HF, Schad F, Schenk G: Viscum album in the therapy of primary inoperable hepatocellular carcinoma (HCC). [Abstract] Gastroenterology 126 (Suppl 2): A-755, A101-A102, 2004.
66. Schaefermeyer G, Schaefermeyer H: Treatment of pancreatic cancer with Viscum album (Iscador): a

retrospective study of 292 patients 1986-1996. Complement Ther Med 6 (4): 172-7, 1998.

67. Kleeberg UR, Brocker EB, Lejeune F, et al.: Adjuvant trial in melanoma patients comparing rIFN-alpha to rIFN-gamma to Iscador to a control group after curative resection of high risk primary (>=3mm) or regional lymphnode metastasis (EORTC 18871). [Abstract] Eur J Cancer 35 (Suppl 4): A-264, s82, 1999.
68. Heiny BM, Albrecht V, Beuth J: Stabilization of quality of life with mistletoe lectin-1-standardized extract in advanced colorectal carcinoma. Onkologe 4 (Suppl 1): S35-9, 1998.
69. Wetzel D, Schäfer M: Results of a randomised placebo-controlled multicentre study with PS76A2 (standardised mistletoe preparation) in patients with breast cancer receiving adjuvant chemotherapy. [Abstract] Phytomedicine 7 (Suppl 2): A-SL-66, 2000.
70. Cho JS, Na KJ, Lee Y, et al.: Chemical Pleurodesis Using Mistletoe Extraction (ABNOVAviscum(®) Injection) for Malignant Pleural Effusion. Ann Thorac Cardiovasc Surg 22 (1): 20-6, 2016. [PUBMED Abstract]
71. Viscum album. In: Homoeopathic Pharmacopoeia Convention of the United States: Homoeopathic Pharmacopoeia of the United States. 2002, Monograph 9444 Visc.

History

Mistletoe has been used for centuries for its medicinal properties.[1-6] It was reportedly used by the Druids and the ancient Greeks, and it appears in legend and folklore as a panacea. It has been used in various forms to treat cancer, epilepsy, infertility, menopausal symptoms, nervous tension, asthma, hypertension, headache, and dermatitis. The use of mistletoe in the treatment of cancer is about 100 years old, and its use in the treatment of other indications is much older. Modern interest in mistletoe as an anticancer treatment began in the 1920s. Most of the results of clinical studies have been published exclusively in German. Refer to the Human/Clinical Studies section of this summary for more information.

Another reported activity of mistletoe that may be relevant to optimum functioning of the immune system in individuals with cancer is stabilization of the DNA in white blood cells, including white blood cells that have been exposed to DNA-damaging chemotherapy drugs.[7-11]

Mistletoe has been shown to stimulate increases in the number and the activity of various types of white blood cells.[2,3,9,11-53] Immune system–enhancing cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor-alpha, are released by white blood cells after exposure to mistletoe extracts.[1,3,7,9-11,14,19,29,33,37,42-46,48-50,52-54] Other evidence suggests that mistletoe exerts its cytotoxic effects by interfering with protein synthesis in target cells [3,4,8,11,33,42-46,52,55-63] and by inducing apoptosis.[3,11,36,42,46,52,64-66] Mistletoe may also serve a bridging function, bringing together immune system effector cells and tumor cells.[18,67]

References

1. Capernaros Z: The golden bough: the case for mistletoe. Eur J Herbal Med 1 (1):19-24, 1994.
2. Mistletoe. In: Murray MT: The Healing Power of Herbs. Prima Publishing, 1995, pp 253-9.
3. Samtleben R, Hajto T, Hostanska K, et al.: Mistletoe lectins as immunostimulants (chemistry,

pharmacology and clinic). In: Wagner H, ed.: Immunomodulatory Agents from Plants. Birkhauser Verlag, 1999, pp 223-41.

4. Olsnes S, Stirpe F, Sandvig K, et al.: Isolation and characterization of viscumin, a toxic lectin from Viscum album L. (mistletoe). J Biol Chem 257 (22): 13263-70, 1982. [PUBMED Abstract]
5. Becker H: Botany of European mistletoe (Viscum album L.). Oncology 43 (Suppl 1): 2-7, 1986. [PUBMED Abstract]
6. Watkins D: A berry Christmas. Nurs Times 93 (51): 28-9, 1997 Dec 17-23. [PUBMED Abstract]
7. Büssing A, Azhari T, Ostendorp H, et al.: Viscum album L. extracts reduce sister chromatid exchanges in cultured peripheral blood mononuclear cells. Eur J Cancer 30A (12): 1836-41, 1994. [PUBMED Abstract]
8. Büssing A, Lehnert A, Schink M, et al.: Effect of Viscum album L. on rapidly proliferating amniotic fluid cells. Sister chromatid exchange frequency and proliferation index. Arzneimittelforschung 45 (1): 81-3, 1995. [PUBMED Abstract]
9. Büssing A, Regnery A, Schweizer K: Effects of Viscum album L. on cyclophosphamide-treated peripheral blood mononuclear cells in vitro: sister chromatid exchanges and activation/proliferation marker expression. Cancer Lett 94 (2): 199-205, 1995. [PUBMED Abstract]
10. Bussing A, Jungmann H, Suzart K, et al.: Suppression of sister chromatid exchange-inducing DNA lesions in cultured peripheral blood mononuclear cells by Viscum album L. J Exp Clin Cancer Res 15 (2): 107-14, 1996.
11. Büssing A, Suzart K, Bergmann J, et al.: Induction of apoptosis in human lymphocytes treated with Viscum album L. is mediated by the mistletoe lectins. Cancer Lett 99 (1): 59-72, 1996. [PUBMED Abstract]
12. Rentea R, Lyon E, Hunter R: Biologic properties of iscador: a Viscum album preparation I. Hyperplasia of the thymic cortex and accelerated regeneration of hematopoietic cells following X-irradiation. Lab Invest 44 (1): 43-8, 1981. [PUBMED Abstract]
13. Bloksma N, Schmiermann P, de Reuver M, et al.: Stimulation of humoral and cellular immunity by Viscum preparations. Planta Med 46 (4): 221-7, 1982. [PUBMED Abstract]
14. Hajto T: Immunomodulatory effects of iscador: a Viscum album preparation. Oncology 43 (Suppl 1): 51-65, 1986. [PUBMED Abstract]
15. Hajto T, Lanzrein C: Natural killer and antibody-dependent cell-mediated cytotoxicity activities and large granular lymphocyte frequencies in Viscum album-treated breast cancer patients. Oncology 43 (2): 93-7, 1986. [PUBMED Abstract]
16. Hamprecht K, Handgretinger R, Voetsch W, et al.: Mediation of human NK-activity by components in extracts of Viscum album. Int J Immunopharmacol 9 (2): 199-209, 1987. [PUBMED Abstract]
17. Hajto T, Hostanska K, Gabius HJ: Modulatory potency of the beta-galactoside-specific lectin from mistletoe extract (Iscador) on the host defense system in vivo in rabbits and patients. Cancer Res 49 (17): 4803-8, 1989. [PUBMED Abstract]
18. Mueller EA, Hamprecht K, Anderer FA: Biochemical characterization of a component in extracts of Viscum album enhancing human NK cytotoxicity. Immunopharmacology 17 (1): 11-8, 1989 Jan-Feb. [PUBMED Abstract]
19. Hajto T, Hostanska K, Frei K, et al.: Increased secretion of tumor necrosis factors alpha, interleukin 1, and interleukin 6 by human mononuclear cells exposed to beta-galactoside-specific lectin from clinically

applied mistletoe extract. Cancer Res 50 (11): 3322-6, 1990. [PUBMED Abstract]

20. Beuth J, Ko HL, Gabius HJ, et al.: Behavior of lymphocyte subsets and expression of activation markers in response to immunotherapy with galactoside-specific lectin from mistletoe in breast cancer patients. Clin Investig 70 (8): 658-61, 1992. [PUBMED Abstract]
21. Kuttan G, Kuttan R: Immunological mechanism of action of the tumor reducing peptide from mistletoe extract (NSC 635089) cellular proliferation. Cancer Lett 66 (2): 123-30, 1992. [PUBMED Abstract]
22. Kuttan G, Kuttan R: Immunomodulatory activity of a peptide isolated from Viscum album extract (NSC 635 089). Immunol Invest 21 (4): 285-96, 1992. [PUBMED Abstract]
23. Gabius HJ, Walzel H, Joshi SS, et al.: The immunomodulatory beta-galactoside-specific lectin from mistletoe: partial sequence analysis, cell and tissue binding, and impact on intracellular biosignalling of monocytic leukemia cells. Anticancer Res 12 (3): 669-75, 1992 May-Jun. [PUBMED Abstract]
24. Beuth J, Ko HL, Tunggal L, et al.: Thymocyte proliferation and maturation in response to galactoside-specific mistletoe lectin-1. In Vivo 7 (5): 407-10, 1993 Sep-Oct. [PUBMED Abstract]
25. Timoshenko AV, Gabius HJ: Efficient induction of superoxide release from human neutrophils by the galactoside-specific lectin from Viscum album. Biol Chem Hoppe Seyler 374 (4): 237-43, 1993. [PUBMED Abstract]
26. Timoshenko AV, Kayser K, Drings P, et al.: Modulation of lectin-triggered superoxide release from neutrophils of tumor patients with and without chemotherapy. Anticancer Res 13 (5C): 1789-92, 1993 Sep-Oct. [PUBMED Abstract]
27. Kuttan G: Tumoricidal activity of mouse peritoneal macrophages treated with Viscum album extract. Immunol Invest 22 (6-7): 431-40, 1993 Aug-Oct. [PUBMED Abstract]
28. Beuth J, Ko HL, Tunggal L, et al.: Immunoprotective activity of the galactoside-specific mistletoe lectin in cortisone-treated BALB/c-mice. In Vivo 8 (6): 989-92, 1994 Nov-Dec. [PUBMED Abstract]
29. Heiny BM, Beuth J: Mistletoe extract standardized for the galactoside-specific lectin (ML-1) induces beta-endorphin release and immunopotentiation in breast cancer patients. Anticancer Res 14 (3B): 1339-42, 1994 May-Jun. [PUBMED Abstract]
30. Stein G, Berg PA: Non-lectin component in a fermented extract from Viscum album L. grown on pines induces proliferation of lymphocytes from healthy and allergic individuals in vitro. Eur J Clin Pharmacol 47 (1): 33-8, 1994. [PUBMED Abstract]
31. Timoshenko AV, Gabius HJ: Influence of the galactoside-specific lectin from Viscum album and its subunits on cell aggregation and selected intracellular parameters of rat thymocytes. Planta Med 61 (2): 130-3, 1995. [PUBMED Abstract]
32. Timoshenko AV, Cherenkevich SN, Gabius HJ: Viscum album agglutinin-induced aggregation of blood cells and the lectin effects on neutrophil function. Biomed Pharmacother 49 (3): 153-8, 1995. [PUBMED Abstract]
33. Hostanska K, Hajto T, Spagnoli GC, et al.: A plant lectin derived from Viscum album induces cytokine gene expression and protein production in cultures of human peripheral blood mononuclear cells. Nat Immun 14 (5-6): 295-304, 1995. [PUBMED Abstract]
34. Beuth J, Stoffel B, Ko HL, et al.: Immunomodulating ability of galactoside-specific lectin standardized and depleted mistletoe extract. Arzneimittelforschung 45 (11): 1240-2, 1995. [PUBMED Abstract]

35. Lenartz D, Stoffel B, Menzel J, et al.: Immunoprotective activity of the galactoside-specific lectin from mistletoe after tumor destructive therapy in glioma patients. Anticancer Res 16 (6B): 3799-802, 1996 Nov-Dec. [PUBMED Abstract]

36. Fischer S, Scheffler A, Kabelitz D: Oligoclonal in vitro response of CD4 T cells to vesicles of mistletoe extracts in mistletoe-treated cancer patients. Cancer Immunol Immunother 44 (3): 150-6, 1997. [PUBMED Abstract]

37. Preisfeld A: Influence of aqueous mistletoe preparations on humoral immune parameters with emphasis on the cytotoxicity of human complement in breast cancer patients. Forsch Komplementarmed 4 (4): 224-8, 1997.

38. Chernyshov VP, Omelchenko LI, Heusser P, et al.: Immunomodulatory actions of Viscum album (Iscador) in children with recurrent respiratory disease as a result of the Chernobyl nuclear accident. Complement Ther Med 5 (3): 141-6, 1997.

39. Heiny BM, Albrecht V, Beuth J: Correlation of immune cell activities and beta-endorphin release in breast carcinoma patients treated with galactose-specific lectin standardized mistletoe extract. Anticancer Res 18 (1B): 583-6, 1998 Jan-Feb. [PUBMED Abstract]

40. Stein GM, Schaller G, Pfüller U, et al.: Characterisation of granulocyte stimulation by thionins from European mistletoe and from wheat. Biochim Biophys Acta 1426 (1): 80-90, 1999. [PUBMED Abstract]

41. Stein GM, Schaller G, Pfüller U, et al.: Thionins from Viscum album L: influence of the viscotoxins on the activation of granulocytes. Anticancer Res 19 (2A): 1037-42, 1999 Mar-Apr. [PUBMED Abstract]

42. Mengs U, Göthel D, Leng-Peschlow E: Mistletoe extracts standardized to mistletoe lectins in oncology: review on current status of preclinical research. Anticancer Res 22 (3): 1399-407, 2002 May-Jun. [PUBMED Abstract]

43. Bocci V: Mistletoe (viscum album) lectins as cytokine inducers and immunoadjuvant in tumor therapy. A review. J Biol Regul Homeost Agents 7 (1): 1-6, 1993 Jan-Mar. [PUBMED Abstract]

44. Gabius HJ, Gabius S, Joshi SS, et al.: From ill-defined extracts to the immunomodulatory lectin: will there be a reason for oncological application of mistletoe? Planta Med 60 (1): 2-7, 1994. [PUBMED Abstract]

45. Zee-Cheng RK: Anticancer research on Loranthaceae plants. Drugs Future 22 (5): 519-30, 1997.

46. Kaegi E: Unconventional therapies for cancer: 3. Iscador. Task Force on Alternative Therapies of the Canadian Breast Cancer Research Initiative. CMAJ 158 (9): 1157-9, 1998. [PUBMED Abstract]

47. Lenartz D, Dott U, Menzel J, et al.: Survival of glioma patients after complementary treatment with galactoside-specific lectin from mistletoe. Anticancer Res 20 (3B): 2073-6, 2000 May-Jun. [PUBMED Abstract]

48. Goebell PJ, Otto T, Suhr J, et al.: Evaluation of an unconventional treatment modality with mistletoe lectin to prevent recurrence of superficial bladder cancer: a randomized phase II trial. J Urol 168 (1): 72-5, 2002. [PUBMED Abstract]

49. Schaefermeyer G, Schaefermeyer H: Treatment of pancreatic cancer with Viscum album (Iscador): a retrospective study of 292 patients 1986-1996. Complement Ther Med 6 (4): 172-7, 1998.

50. Kunze E, Schulz H, Gabius HJ: Inability of galactoside-specific mistletoe lectin to inhibit N-methyl-N-nitrosourea-induced tumor development in the urinary bladder of rats and to mediate a local cellular immune response after long-term administration. J Cancer Res Clin Oncol 124 (2): 73-87,

1998. [PUBMED Abstract]

51. Kunze E, Schulz H, Adamek M, et al.: Long-term administration of galactoside-specific mistletoe lectin in an animal model: no protection against N-butyl-N-(4-hydroxybutyl)-nitrosamine-induced urinary bladder carcinogenesis in rats and no induction of a relevant local cellular immune response. J Cancer Res Clin Oncol 126 (3): 125-38, 2000. [PUBMED Abstract]

52. Mengs U, Schwarz T, Bulitta M, et al.: Antitumoral effects of an intravesically applied aqueous mistletoe extract on urinary bladder carcinoma MB49 in mice. Anticancer Res 20 (5B): 3565-8, 2000 Sep-Oct. [PUBMED Abstract]

53. Stauder H, Kreuser ED: Mistletoe extracts standardised in terms of mistletoe lectins (ML I) in oncology: current state of clinical research. Onkologie 25 (4): 374-80, 2002. [PUBMED Abstract]

54. Kleijnen J, Knipschild P: Mistletoe treatment for cancer: review of controlled trials in humans. Phytomedicine 1: 255-60, 1994.

55. Stirpe F, Sandvig K, Olsnes S, et al.: Action of viscumin, a toxic lectin from mistletoe, on cells in culture. J Biol Chem 257 (22): 13271-7, 1982. [PUBMED Abstract]

56. Walzel H, Jonas L, Rosin T, et al.: Relationship between internalization kinetics and cytotoxicity of mistletoe lectin I to L1210 leukaemia cells. Folia Biol (Praha) 36 (3-4): 181-8, 1990. [PUBMED Abstract]

57. Franz H: Mistletoe lectins and their A and B chains. Oncology 43 (Suppl 1): 23-34, 1986. [PUBMED Abstract]

58. Sweeney EC, Palmer RA, Pfüller U: Crystallization of the ribosome inactivating protein ML1 from Viscum album (mistletoe) complexed with beta-D-galactose. J Mol Biol 234 (4): 1279-81, 1993. [PUBMED Abstract]

59. Jung ML, Baudino S, Ribéreau-Gayon G, et al.: Characterization of cytotoxic proteins from mistletoe (Viscum album L.). Cancer Lett 51 (2): 103-8, 1990. [PUBMED Abstract]

60. Gabius HJ, Darro F, Remmelink M, et al.: Evidence for stimulation of tumor proliferation in cell lines and histotypic cultures by clinically relevant low doses of the galactoside-binding mistletoe lectin, a component of proprietary extracts. Cancer Invest 19 (2): 114-26, 2001. [PUBMED Abstract]

61. Dietrich JB, Ribéreau-Gayon G, Jung ML, et al.: Identity of the N-terminal sequences of the three A chains of mistletoe (Viscum album L.) lectins: homology with ricin-like plant toxins and single-chain ribosome-inhibiting proteins. Anticancer Drugs 3 (5): 507-11, 1992. [PUBMED Abstract]

62. Jäggy C, Musielski H, Urech K, et al.: Quantitative determination of lectins in mistletoe preparations. Arzneimittelforschung 45 (8): 905-9, 1995. [PUBMED Abstract]

63. Burger AM, Mengs U, Schüler JB, et al.: Anticancer activity of an aqueous mistletoe extract (AME) in syngeneic murine tumor models. Anticancer Res 21 (3B): 1965-8, 2001 May-Jun. [PUBMED Abstract]

64. Janssen O, Scheffler A, Kabelitz D: In vitro effects of mistletoe extracts and mistletoe lectins. Cytotoxicity towards tumor cells due to the induction of programmed cell death (apoptosis). Arzneimittelforschung 43 (11): 1221-7, 1993. [PUBMED Abstract]

65. Zarkovic N, Vukovic T, Loncaric I, et al.: An overview on anticancer activities of the Viscum album extract Isorel. Cancer Biother Radiopharm 16 (1): 55-62, 2001. [PUBMED Abstract]

66. Maier G, Fiebig HH: Absence of tumor growth stimulation in a panel of 16 human tumor cell lines by mistletoe extracts in vitro. Anticancer Drugs 13 (4): 373-9, 2002. [PUBMED Abstract]

67. Mueller EA, Anderer FA: Chemical specificity of effector cell/tumor cell bridging by a Viscum album rhamnogalacturonan enhancing cytotoxicity of human NK cells. Immunopharmacology 19 (1): 69-77, 1990 Jan-Feb. [PUBMED Abstract]

Laboratory/Animal/Preclinical Studies

The immune system–stimulating and cytotoxic properties of mistletoe have been investigated in laboratory and animal studies.

Viscotoxins and lectins have been investigated as active components in mistletoe; most research has focused on the lectins.[1-9] Purified mistletoe lectins have demonstrated cytotoxic and immune system–stimulating activities. Four different lectins have been identified in mistletoe extracts as follows:

- ML-1.
- ML-2.
- ML-3.
- *Viscum album* chitin-binding agglutinin.

ML-1 (or viscumin) may be responsible for many of mistletoe's biological effects. When a laboratory method was used to selectively deplete ML-1 from *Viscum album* extracts, their cytotoxic and immune system–stimulating properties were markedly reduced.[10,11] It should be noted that fermentation eliminates most of the ML-1 in mistletoe extracts. Iscador, and other fermented mistletoe extracts, contain only the mistletoe lectins ML-2 and ML-3, whereas the proteins of the ML-1 complex are missing.[12-14] Polysaccharide and oligosaccharide components of mistletoe extracts with substantial immune-stimulating properties have been reviewed.[15,16]

The molecular structure of ML-1 consists of an alpha chain and a beta chain, which can be separated from one another.[1,6-9,13,17,18] Each chain type appears to mediate a subset of the activities described for the intact lectin. Cytotoxicity is associated mainly with the alpha chain. In laboratory studies, the ML-1 alpha chain has been coupled to monoclonal antibodies to produce immunotoxins that target and kill specific cell types.[19-21]

Recombinant ML-1, rML (also known as rViscumin or aviscumine) appears to have the same efficacy as plant-based ML-1 in laboratory studies.[22] Because this is not an extract of mistletoe, it is out of the purview of this summary.

The beta chain of ML-1 is responsible for binding to the surface of a target cell.[23] Studies of mistletoe lectin binding to cancer cells have examined whether the extent of cell binding can predict disease outcome or survival. Studies show that the prognostic value of ML-1 binding depends on the type of cancer.[24] For human breast cancer cells, the amount of lectin-bound cells correlates positively with disease outcome. However, for human adenocarcinoma of the lung, there is no correlation between the amount of lectin-bound cells and disease survival.[25] Though much research has looked at this particular aspect, there have not been studies that directly link the concentration of that component to any clinical activity of mistletoe.

Laboratory studies have shown that mistletoe extracts can stimulate the activity of white blood cells *in vitro* and cause them to release molecules thought to be important for anticancer immune responses.[4,6,8,9,17,26-33] In addition, mistletoe extracts have demonstrated cytotoxic activity against a variety of mouse, rat, and human cancer cells *in vitro*.[1,8,23,34-37]

There are conflicting reports concerning the stimulation of cancer cell growth *in vitro*. In one study, the *in vitro* growth of several types of human cancer cells was stimulated by treatment with low doses of the purified lectin ML-1.[1] However, various other studies found that ML-1 and mistletoe extracts did not induce cell proliferation.[38,39]

Preclinical studies demonstrating biological effects on cancer cell lines and animal models are summarized in Table 1 and Table 2.

Table 1. *In Vitro* Studies[a]

Iscador		
Cell Line	**Outcome**	**Reference**
Various human cancer cell lines	Iscador preparations containing a high lectin concentration (15 µg/mL) showed >70% growth inhibition in the mammary cancer cell line (MAXF 401NL) compared with untreated control cells; 30%–70% growth inhibition in three tumor cell lines (leukemia RPMI 8226, non-small cell lung LXFE 66NL, and uterine UXF 1138L) for IscadorM and in seven tumor cell lines (central nervous system SF268, gastric GXF 251L, non-small cell lung LXFE 66NL and LXFL 529L, prostate PC3M, renal RXF 944L, and uterine UXF 1138L) for IscadorQu	[35]

IscadorQu = IscadorQ; ML-1 = mistletoe extracts with mistletoe lectins I.

[a]Refer to text and the NCI Dictionary of Cancer Terms for additional information and definition of terms.

Human medulloblastoma cells Daoy, D341, D425, and UW 228-2	*Viscum album* preparations (0.1 µg/mL–100 µg/mL) induced cell death through apoptosis. Growth-inhibition correlated with the lectin content of the used preparation	[37]
Various human cancer cell lines (central nervous system SF268; gastric GXF 251; lung H460, LXFA 629L, LXFE 66NL, LXFL 529L; leukemia and lymphoma CCRFCEM, MOLT-4, HL-60, K562, U937, RPMI 8226; mammary MCF7, MAXF 401NL; melanoma HT144, MALME-3M, SK-MEL28, MEXF 462NL, MEXF 514L; prostate PC3M; renal RXF 393NL, RXF 944L; sarcoma Hs729, SK-LMS-1, SK-UT-1B; and uterus UXF 1138L)	IscadorM and IscadorQu with a high lectin content demonstrated antitumor activity *in vitro* at high test concentrations (15–150 µg/mL)	[38]
Human cell lines: HCC1937, HCC1143 (breast), PA-TU-8902 (pancreas), DU145 (prostate), NCI-H460 (lung)	Cell proliferation inhibition was detected with a mistletoe dose at 100 µg/mL in cell lines PA-TU-8902 and NCI-H460, and a dose at ≥10 µg/mL in cell lines HCC1937, HCC1143, and DU145	[40]
Glioblastoma cells: LNT-229, LN-308	Cell growth was reduced with IscadorQ and IscadorM at lectin concentrations of 100 µg/mL	[41]
Helixor		
Cell Line	**Outcome**	**Reference**
Various human cancer cell lines	Helixor mistletoe preparations (15 µg/mL–150 µg/mL) and ML-1 (10	[39]

IscadorQu = IscadorQ; ML-1 = mistletoe extracts with mistletoe lectins I.

[a]Refer to text and the NCI Dictionary of Cancer Terms for additional information and definition of terms.

	ng/mL–100 ng/mL) did not induce cell proliferation	
abnobaVISCUM		
Cell Line	**Outcome**	**Reference**
Human tumor cell lines (B-cell hybridomas, P815, EL-4, Ke37, MOLT-4, and U937)	Growth arrest was caused by the induction of apoptosis (50% of U937 cells at 100 ng/mL of ML-1 and 40% of B-cell hybridomas and EL-4 cells at concentrations as low as 1 ng/mL of ML-1)	[10]

IscadorQu = IscadorQ; ML-1 = mistletoe extracts with mistletoe lectins I.

[a]Refer to text and the NCI Dictionary of Cancer Terms for additional information and definition of terms.

Studies of the ability of mistletoe to inhibit cancer cell growth in animals have yielded mixed and inconsistent results.[5-9,36,42-50] In most of these studies, mistletoe extracts were administered either by subcutaneous injection or by intraperitoneal injection; some of the differences in results may have resulted from the difference in route of administration. For example, IscadorM administration was associated with a prolonged survival of female Swiss mice when the route of administration was intraperitoneal [51] but not when the route was subcutaneous.[52] Other differences between these two studies were the number of cells used in the Ehrlich ascites inoculum and the doses of IscadorM administered.

Table 2. *In Vivo* Studies[a]

Iscador		
Animal Model	**Outcome**	**Reference**

ALL = acute lymphoblastic leukemia; ME-A = mistletoe extracts (fir tree *Abies*); ME-M = mistletoe extracts (apple tree *Malus*); ML-1 = mistletoe extracts with mistletoe lectins I; ML-3 = mistletoe extracts with mistletoe lectins III; MT-A = mistletoe extracts obtained from fir trees; MT-P = mistletoe extracts obtained from pine trees; NK = natural killer.

[a]Refer to text and the NCI Dictionary of Cancer Terms for additional information and definition of terms.

Mice	Antiproliferative and antimetastatic effects in melanoma cell line MV3 were only achieved with low-dose ML-1 (30 ng/kg body weight) and not with higher doses (150 ng/kg and 500 ng/kg); increased number of infiltrating dendritic cells suggests stimulation of the immune system	[44]
Mice	Viscum album extract (20 µg/mouse/d) mediated inhibition of B16F1 melanoma cells tumor growth was associated with immunomodulation via induction of IL-12 secretion leading to enhanced T-cell and NK-cell functions	[45]
Mice	Organ colonization was investigated on day 14 after RAW 117 H 10 lymphosarcoma cell and L-1 sarcoma cell inoculation and demonstrated statistically significant ($P < .05$) reductions of experimental liver and lung metastases for standardized aqueous mistletoe extract–treated mice (2 µg, 20 µg, 100 µg, and 500 µg per mouse)	[47]
Mice (Nude and VMDk mice)	Glioblastoma tumor growth was reduced (cell lines LNT-229 and LN-308), the expression of genes associated with tumor	[41]

ALL = acute lymphoblastic leukemia; ME-A = mistletoe extracts (fir tree *Abies*); ME-M = mistletoe extracts (apple tree *Malus*); ML-1 = mistletoe extracts with mistletoe lectins I; ML-3 = mistletoe extracts with mistletoe lectins III; MT-A = mistletoe extracts obtained from fir trees; MT-P = mistletoe extracts obtained from pine trees; NK = natural killer.

[a]Refer to text and the NCI Dictionary of Cancer Terms for additional information and definition of terms.

	progression was reduced, and NK cell mediated glioblastoma cell lysis was enhanced when IscadorQ and IscadorM 100 µg/mL was administered by an intratumoral injection	
BDF and Swiss albino mice	Treatment with IscadorM (50 mg/kg/d and 100 mg/kg/d) increased the survival time of mice that had been implanted with Ehrlich ascites mouse cancer cells, but not L1210 leukemia or B16 melanoma cancer cells	[51]
Swiss albino mice	No antitumor effect or improvement in survival was observed when IscadorM (15.75 mg, 750 mg, 10.5 mg, 500 mg) was used to treat rats bearing chemically induced mammary carcinomas or tumors formed from rat Walker 256 carcinosarcoma cells; IscadorM (5 mg, 200 mg, 150 mg, 3.75 mg) was also not effective in treating mice that had been injected with Ehrlich ascites cells; in addition, IscadorP (135 mg) was found ineffective in treating rats with tumors formed from rat L5222 leukemia cells	[52]
Helixor		

ALL = acute lymphoblastic leukemia; ME-A = mistletoe extracts (fir tree *Abies*); ME-M = mistletoe extracts (apple tree *Malus*); ML-1 = mistletoe extracts with mistletoe lectins I; ML-3 = mistletoe extracts with mistletoe lectins III; MT-A = mistletoe extracts obtained from fir trees; MT-P = mistletoe extracts obtained from pine trees; NK = natural killer.

[a]Refer to text and the NCI Dictionary of Cancer Terms for additional information and definition of terms.

Animal Model	Outcome	Reference
SCID mice	Despite a considerably lower ML-3 content, MT-A (50 mg/kg and 100 mg/kg) was more effective and less toxic than MT-P (50 mg/kg) in a human acute lymphoblastic leukemia cell line (NALM-6); both were given intraperitoneally in mice inoculated with human ALL	[43]
Human ductal breast carcinoma cell line BT474	As compared with tumors of control mice, tumors of the ME-A– and ME-M–treated groups (5 mg intratumoral injection) showed a decreased cell proliferation rate, as well as an increased cell necrosis and apoptosis rate	[46]

abnobaVISCUM

Animal Model	Outcome	Reference
Nude mice	Intratumoral injections of mistletoe extract (abnobaVISCUM Fraxini-2, 8 mg/kg body weight and lectin at 5.3 µg/kg body weight) demonstrated more antitumor activity than did intravenous gemcitabine when injected into mice bearing xenografts of	[53]

ALL = acute lymphoblastic leukemia; ME-A = mistletoe extracts (fir tree *Abies*); ME-M = mistletoe extracts (apple tree *Malus*); ML-1 = mistletoe extracts with mistletoe lectins I; ML-3 = mistletoe extracts with mistletoe lectins III; MT-A = mistletoe extracts obtained from fir trees; MT-P = mistletoe extracts obtained from pine trees; NK = natural killer.

[a]Refer to text and the NCI Dictionary of Cancer Terms for additional information and definition of terms.

	human pancreatic adenocarcinoma cancer (PAXF 736)	

Isorel

Animal Model	Outcome	Reference
Mice	In mice transplanted with fibrosarcoma (CMC-2), when IsorelM (140 mg/kg) was used alone, no effect on either tumor growth or animal survival was observed. When IsorelM (140 mg/kg) was combined with x-ray therapy of tumors, there was substantial improvements in survival of mice compared with survival of mice treated with x-ray therapy (43 Gy) alone	[54]

Eurixor

Animal Model	Outcome	Reference
Mice	Aqueous mistletoe extract (30 ng/mL or 300 ng/mL) showed antitumoral activity on urinary bladder carcinoma (MB49) in mice, which was considered to be mainly caused by the cytotoxic properties of mistletoe lectins	[6]

ALL = acute lymphoblastic leukemia; ME-A = mistletoe extracts (fir tree *Abies*); ME-M = mistletoe extracts (apple tree *Malus*); ML-1 = mistletoe extracts with mistletoe lectins I; ML-3 = mistletoe extracts with mistletoe lectins III; MT-A = mistletoe extracts obtained from fir trees; MT-P = mistletoe extracts obtained from pine trees; NK = natural killer.

[a]Refer to text and the NCI Dictionary of Cancer Terms for additional information and definition of terms.

Lektinol

Animal Model	Outcome	Reference
Mice	Treatment with Lektinol (0.3, 3, 30, or 300 ng/mL/kg/d) slowed the growth of tumors formed in mice from implants of three types of mouse cancers (colon adenocarcinoma 38, Renca renal cell carcinoma, and F9 testicular carcinoma) but not from two other mouse cancers (B16 melanoma and Lewis lung carcinoma)	[7]

ALL = acute lymphoblastic leukemia; ME-A = mistletoe extracts (fir tree *Abies*); ME-M = mistletoe extracts (apple tree *Malus*); ML-1 = mistletoe extracts with mistletoe lectins I; ML-3 = mistletoe extracts with mistletoe lectins III; MT-A = mistletoe extracts obtained from fir trees; MT-P = mistletoe extracts obtained from pine trees; NK = natural killer.

[a]Refer to text and the NCI Dictionary of Cancer Terms for additional information and definition of terms.

References

1. Gabius HJ, Darro F, Remmelink M, et al.: Evidence for stimulation of tumor proliferation in cell lines and histotypic cultures by clinically relevant low doses of the galactoside-binding mistletoe lectin, a component of proprietary extracts. Cancer Invest 19 (2): 114-26, 2001. [PUBMED Abstract]
2. Lenartz D, Dott U, Menzel J, et al.: Survival of glioma patients after complementary treatment with galactoside-specific lectin from mistletoe. Anticancer Res 20 (3B): 2073-6, 2000 May-Jun. [PUBMED Abstract]
3. Steuer-Vogt MK, Bonkowsky V, Ambrosch P, et al.: The effect of an adjuvant mistletoe treatment programme in resected head and neck cancer patients: a randomised controlled clinical trial. Eur J Cancer 37 (1): 23-31, 2001. [PUBMED Abstract]
4. Goebell PJ, Otto T, Suhr J, et al.: Evaluation of an unconventional treatment modality with mistletoe lectin to prevent recurrence of superficial bladder cancer: a randomized phase II trial. J Urol 168 (1): 72-5, 2002. [PUBMED Abstract]
5. Kunze E, Schulz H, Adamek M, et al.: Long-term administration of galactoside-specific mistletoe lectin in an animal model: no protection against N-butyl-N-(4-hydroxybutyl)-nitrosamine-induced urinary bladder carcinogenesis in rats and no induction of a relevant local cellular immune response. J Cancer Res Clin Oncol 126 (3): 125-38, 2000. [PUBMED Abstract]

6. Mengs U, Schwarz T, Bulitta M, et al.: Antitumoral effects of an intravesically applied aqueous mistletoe extract on urinary bladder carcinoma MB49 in mice. Anticancer Res 20 (5B): 3565-8, 2000 Sep-Oct. [PUBMED Abstract]
7. Burger AM, Mengs U, Schüler JB, et al.: Anticancer activity of an aqueous mistletoe extract (AME) in syngeneic murine tumor models. Anticancer Res 21 (3B): 1965-8, 2001 May-Jun. [PUBMED Abstract]
8. Mengs U, Göthel D, Leng-Peschlow E: Mistletoe extracts standardized to mistletoe lectins in oncology: review on current status of preclinical research. Anticancer Res 22 (3): 1399-407, 2002 May-Jun. [PUBMED Abstract]
9. Samtleben R, Hajto T, Hostanska K, et al.: Mistletoe lectins as immunostimulants (chemistry, pharmacology and clinic). In: Wagner H, ed.: Immunomodulatory Agents from Plants. Birkhauser Verlag, 1999, pp 223-41.
10. Janssen O, Scheffler A, Kabelitz D: In vitro effects of mistletoe extracts and mistletoe lectins. Cytotoxicity towards tumor cells due to the induction of programmed cell death (apoptosis). Arzneimittelforschung 43 (11): 1221-7, 1993. [PUBMED Abstract]
11. Beuth J, Stoffel B, Ko HL, et al.: Immunomodulating ability of galactoside-specific lectin standardized and depleted mistletoe extract. Arzneimittelforschung 45 (11): 1240-2, 1995. [PUBMED Abstract]
12. Wagner H, Jordan E, Feil B: Studies on the standardization of mistletoe preparations. Oncology 43 (Suppl 1): 16-22, 1986. [PUBMED Abstract]
13. Mistletoe. In: Murray MT: The Healing Power of Herbs. Prima Publishing, 1995, pp 253-9.
14. Jäggy C, Musielski H, Urech K, et al.: Quantitative determination of lectins in mistletoe preparations. Arzneimittelforschung 45 (8): 905-9, 1995. [PUBMED Abstract]
15. Stein GM, Büssing A, Schietzel M: Stimulation of the maturation of dendritic cells in vitro by a fermented mistletoe extract. Anticancer Res 22 (6C): 4215-9, 2002 Nov-Dec. [PUBMED Abstract]
16. Lyu SY, Kwon YJ, Joo HJ, et al.: Preparation of alginate/chitosan microcapsules and enteric coated granules of mistletoe lectin. Arch Pharm Res 27 (1): 118-26, 2004. [PUBMED Abstract]
17. Timoshenko AV, Gabius HJ: Efficient induction of superoxide release from human neutrophils by the galactoside-specific lectin from Viscum album. Biol Chem Hoppe Seyler 374 (4): 237-43, 1993. [PUBMED Abstract]
18. Dietrich JB, Ribéreau-Gayon G, Jung ML, et al.: Identity of the N-terminal sequences of the three A chains of mistletoe (Viscum album L.) lectins: homology with ricin-like plant toxins and single-chain ribosome-inhibiting proteins. Anticancer Drugs 3 (5): 507-11, 1992. [PUBMED Abstract]
19. Wiedłocha A, Sandvig K, Walzel H, et al.: Internalization and action of an immunotoxin containing mistletoe lectin A-chain. Cancer Res 51 (3): 916-20, 1991. [PUBMED Abstract]
20. Tonevitsky AG, Toptygin AYu, Pfuller U, et al.: Immunotoxin with mistletoe lectin I A-chain and ricin A-chain directed against CD5 antigen of human T-lymphocytes; comparison of efficiency and specificity. Int J Immunopharmacol 13 (7): 1037-41, 1991. [PUBMED Abstract]
21. Bocci V: Mistletoe (viscum album) lectins as cytokine inducers and immunoadjuvant in tumor therapy. A review. J Biol Regul Homeost Agents 7 (1): 1-6, 1993 Jan-Mar. [PUBMED Abstract]
22. Habeck M: Mistletoe compound enters clinical trials. Drug Discov Today 8 (2): 52-3, 2003. [PUBMED Abstract]

23. Müthing J, Meisen I, Kniep B, et al.: Tumor-associated CD75s gangliosides and CD75s-bearing glycoproteins with Neu5Acalpha2-6Galbeta1-4GlcNAc-residues are receptors for the anticancer drug rViscumin. FASEB J 19 (1): 103-5, 2005. [PUBMED Abstract]

24. Fritz P, Dippon J, Kierschke T, et al.: Impact of mistletoe lectin binding in breast cancer. Anticancer Res 24 (2C): 1187-92, 2004 Mar-Apr. [PUBMED Abstract]

25. Blonski K, Schumacher U, Burkholder I, et al.: Binding of recombinant mistletoe lectin (aviscumine) to resected human adenocarcinoma of the lung. Anticancer Res 25 (5): 3303-7, 2005 Sep-Oct. [PUBMED Abstract]

26. Timoshenko AV, Kayser K, Drings P, et al.: Modulation of lectin-triggered superoxide release from neutrophils of tumor patients with and without chemotherapy. Anticancer Res 13 (5C): 1789-92, 1993 Sep-Oct. [PUBMED Abstract]

27. Timoshenko AV, Gabius HJ: Influence of the galactoside-specific lectin from Viscum album and its subunits on cell aggregation and selected intracellular parameters of rat thymocytes. Planta Med 61 (2): 130-3, 1995. [PUBMED Abstract]

28. Timoshenko AV, Cherenkevich SN, Gabius HJ: Viscum album agglutinin-induced aggregation of blood cells and the lectin effects on neutrophil function. Biomed Pharmacother 49 (3): 153-8, 1995. [PUBMED Abstract]

29. Hostanska K, Hajto T, Spagnoli GC, et al.: A plant lectin derived from Viscum album induces cytokine gene expression and protein production in cultures of human peripheral blood mononuclear cells. Nat Immun 14 (5-6): 295-304, 1995. [PUBMED Abstract]

30. Fischer S, Scheffler A, Kabelitz D: Oligoclonal in vitro response of CD4 T cells to vesicles of mistletoe extracts in mistletoe-treated cancer patients. Cancer Immunol Immunother 44 (3): 150-6, 1997. [PUBMED Abstract]

31. Stein GM, Schaller G, Pfüller U, et al.: Characterisation of granulocyte stimulation by thionins from European mistletoe and from wheat. Biochim Biophys Acta 1426 (1): 80-90, 1999. [PUBMED Abstract]

32. Stein GM, Schaller G, Pfüller U, et al.: Thionins from Viscum album L: influence of the viscotoxins on the activation of granulocytes. Anticancer Res 19 (2A): 1037-42, 1999 Mar-Apr. [PUBMED Abstract]

33. Hallek M: Interleukin-6-mediated cell growth in multiple myeloma--a role for Viscum album extracts? Onkologie 28 (8-9): 387, 2005. [PUBMED Abstract]

34. Schaller G, Urech K, Giannattasio M: Cytotoxicity of different viscotoxins and extracts from the European subspecies Viscum album L. Phytother Res 10 (6): 473-7, 1996.

35. Maier G, Fiebig HH: Absence of tumor growth stimulation in a panel of 16 human tumor cell lines by mistletoe extracts in vitro. Anticancer Drugs 13 (4): 373-9, 2002. [PUBMED Abstract]

36. Zarkovic N, Vukovic T, Loncaric I, et al.: An overview on anticancer activities of the Viscum album extract Isorel. Cancer Biother Radiopharm 16 (1): 55-62, 2001. [PUBMED Abstract]

37. Zuzak TJ, Rist L, Eggenschwiler J, et al.: Paediatric medulloblastoma cells are susceptible to Viscum album (Mistletoe) preparations. Anticancer Res 26 (5A): 3485-92, 2006 Sep-Oct. [PUBMED Abstract]

38. Kelter G, Fiebig HH: Absence of tumor growth stimulation in a panel of 26 human tumor cell lines by mistletoe (Viscum album L.) extracts Iscador in vitro. Arzneimittelforschung 56 (6A): 435-40, 2006. [PUBMED Abstract]

39. Kelter G, Schierholz JM, Fischer IU, et al.: Cytotoxic activity and absence of tumor growth stimulation of standardized mistletoe extracts in human tumor models in vitro. Anticancer Res 27 (1A): 223-33, 2007 Jan-Feb. [PUBMED Abstract]

40. Weissenstein U, Kunz M, Urech K, et al.: Interaction of standardized mistletoe (Viscum album) extracts with chemotherapeutic drugs regarding cytostatic and cytotoxic effects in vitro. BMC Complement Altern Med 14: 6, 2014. [PUBMED Abstract]

41. Podlech O, Harter PN, Mittelbronn M, et al.: Fermented mistletoe extract as a multimodal antitumoral agent in gliomas. Evid Based Complement Alternat Med 2012: 501796, 2012. [PUBMED Abstract]

42. Cebović T, Spasić S, Popović M: Cytotoxic effects of the Viscum album L. extract on Ehrlich tumour cells in vivo. Phytother Res 22 (8): 1097-103, 2008. [PUBMED Abstract]

43. Seifert G, Jesse P, Laengler A, et al.: Molecular mechanisms of mistletoe plant extract-induced apoptosis in acute lymphoblastic leukemia in vivo and in vitro. Cancer Lett 264 (2): 218-28, 2008. [PUBMED Abstract]

44. Thies A, Dautel P, Meyer A, et al.: Low-dose mistletoe lectin-I reduces melanoma growth and spread in a scid mouse xenograft model. Br J Cancer 98 (1): 106-12, 2008. [PUBMED Abstract]

45. Van Huyen JP, Delignat S, Bayry J, et al.: Interleukin-12 is associated with the in vivo anti-tumor effect of mistletoe extracts in B16 mouse melanoma. Cancer Lett 243 (1): 32-7, 2006. [PUBMED Abstract]

46. Beuth J, Ko HL, Schneider H, et al.: Intratumoral application of standardized mistletoe extracts down regulates tumor weight via decreased cell proliferation, increased apoptosis and necrosis in a murine model. Anticancer Res 26 (6B): 4451-6, 2006 Nov-Dec. [PUBMED Abstract]

47. Braun JM, Ko HL, Schierholz JM, et al.: Standardized mistletoe extract augments immune response and down-regulates local and metastatic tumor growth in murine models. Anticancer Res 22 (6C): 4187-90, 2002 Nov-Dec. [PUBMED Abstract]

48. Pryme IF, Bardocz S, Pusztai A, et al.: Dietary mistletoe lectin supplementation and reduced growth of a murine non-Hodgkin lymphoma. Histol Histopathol 17 (1): 261-71, 2002. [PUBMED Abstract]

49. Elsässer-Beile U, Ruhnau T, Freudenberg N, et al.: Antitumoral effect of recombinant mistletoe lectin on chemically induced urinary bladder carcinogenesis in a rat model. Cancer 91 (5): 998-1004, 2001. [PUBMED Abstract]

50. Stauder H, Kreuser ED: Mistletoe extracts standardised in terms of mistletoe lectins (ML I) in oncology: current state of clinical research. Onkologie 25 (4): 374-80, 2002. [PUBMED Abstract]

51. Khwaja TA, Dias CB, Pentecost S: Recent studies on the anticancer activities of mistletoe (Viscum album) and its alkaloids. Oncology 43 (Suppl 1): 42-50, 1986. [PUBMED Abstract]

52. Berger M, Schmähl D: Studies on the tumor-inhibiting efficacy of Iscador in experimental animal tumors. J Cancer Res Clin Oncol 105 (3): 262-5, 1983. [PUBMED Abstract]

53. Rostock M, Huber R, Greiner T, et al.: Anticancer activity of a lectin-rich mistletoe extract injected intratumorally into human pancreatic cancer xenografts. Anticancer Res 25 (3B): 1969-75, 2005 May-Jun. [PUBMED Abstract]

54. Jurin M, Zarković N, Hrzenjak M, et al.: Antitumorous and immunomodulatory effects of the Viscum album L. preparation Isorel. Oncology 50 (6): 393-8, 1993 Nov-Dec. [PUBMED Abstract]

Human/Clinical Studies

Mistletoe has been evaluated as a treatment for people with cancer in numerous clinical studies.[1-20]

The mistletoe extracts and products studied in clinical trials were Iscador, Eurixor, Helixor, Lektinol, Isorel, abnobaVISCUM,[21] and recombinant lectin ML-1 (refer to the appropriate sections and tables at the end of this section for more information).

The findings from more than 50 clinical trials of mistletoe extracts in patients with cancer have been published, and several systematic reviews and meta-analyses of the results of these studies have been performed. Three of the most recent systematic reviews addressed quality of life (QOL), survival, and symptom relief in patients with various cancer types.[18,20,22] Most studies reported an improvement in QOL, as did a noncontrolled, nonrandomized, real-world study that analyzed patient registry data.[23]

In one systematic review that examined 26 randomized controlled trials (RCTs), 22 trials reported an improvement in QOL. All 10 of the nonRCTs also reported the same benefit. Improvement in fatigue, nausea and vomiting, depression, emotional well-being, and concentration were reported. Some of the studies were well designed, while others reported weaknesses.[22]

Tumor response, QOL, and psychological distress were measured in a review of 21 RCTs of various cancers in which different mistletoe preparations were used either alone, with chemotherapy, or with radiation therapy.[18] Survival times were included in 13 of the studies. Most of the studies reported benefits for patients, although this review was limited by small sample size and methodological weaknesses. Thus, the authors were unable to suggest practice guidelines for the use of mistletoe.

The oldest of these three reviews investigated the results of 10 RCTs that used a variety of mistletoe extracts in patients with various malignancies. There was no difference in survival or other benefits for cancer patients who received mistletoe. Therefore, mistletoe was not recommended as a curative or supportive care therapy.[20]

A systematic review of all controlled clinical studies of mistletoe found consistent improvement in chemotherapy-associated fatigue as well as other QOL measures.[22]

Although mistletoe was found to be therapeutically effective in most of the reported studies, many of the studies had one or more major design weaknesses as mentioned above that raised doubts about the reliability of the findings. These weaknesses include the following:

- Registration of small numbers of patients.
- Presence of large numbers of patients who either were not evaluable or were otherwise excluded from the analyses.
- Failure to adequately document mistletoe use, mistletoe dose, and/or interruptions of mistletoe use.
- Absence of control subjects or use of historical control subjects.
- Use of inadequate randomization procedures.
- Absence of treatment blinding.
- Extensive use of subset analysis.

- The measurement of mean as opposed to median survival.

In addition, evaluation of the studies is often hindered by incomplete descriptions of the study design and by incomplete reporting of clinical data, including data about previous and concurrent therapies received by the patients. Note: In studies with small numbers of patients, the mean survival time can be greatly exaggerated if one or more patients exhibit unusually long survival; median survival, therefore, is a less biased measure.

A selection of studies is discussed below, organized by the type of mistletoe extract used. Eurixor, Isorel, and Vysorel are no longer available on the market for sale.

Iscador

An interim analysis of a randomized phase III trial reported on 220 patients with locally advanced or metastatic pancreatic cancer.[24] Patients received best supportive care and were randomly assigned to receive either IscadorQu or no antineoplastic therapy (control). Patients were stratified according to tumor stage, age, and performance status. Iscador was administered subcutaneously in a dose-escalating manner from 0.01 mg to 10 mg three times per week. Treatment with Iscador demonstrated a significant enhancement of overall survival (OS) (4.8 months vs. 2.7 months for IscadorQu patients vs. control patients, respectively; prognosis-adjusted hazard ratio [HR], 0.49; $P < .0001$).

The independent data monitoring committee that reviewed the interim analysis results recommended termination of the trial because of statistically significant superiority of survival in the treatment group compared with the control group. Further analysis of a subset of the 220 patients enrolled demonstrated improved QOL symptoms (pain, fatigue, weight loss, nausea, diarrhea, and anxiety) in the treatment group compared with the control group.[25]

A three-arm, randomized phase III trial that involved 408 patients with previously untreated, inoperable non-small cell lung cancer was conducted between 1978 and 1987.[26] Patients were randomly assigned to one of the following treatments:

- Subcutaneous injection 3 times a week with IscadorU or IscadorQu (refer to the General Information section of this summary for more information); the concentration of mistletoe was increased during a seven-injection sequence or cycle, followed by a 3-day pause, and then the process was repeated; IscadorU was administered for two cycles, followed by two cycles of IscadorQu; both mistletoe preparations contained mercury).
- Intramuscular injection once a week with Polyerga Neu, which is a sheep spleen glycopeptide that is reported to be an immunostimulant and an inhibitor of tumor cell glycolysis.
- Intramuscular injection once a week with a vitamin B mixture, which served as a placebo.

Complete follow-up information was available for 337 patients, and 312 patients (105 Iscador treated, 100 Polyerga Neu treated, and 107 placebo treated) were included in the survival analysis. No statistically significant differences in survival were found between the three groups. Median survival for the Iscador group was 9.1 months; for the Polyerga Neu group, it was 9.0 months; and for the placebo group, it was 7.6 months. The researchers reported that 11.5% of the patients in the Iscador group survived 2 years from the time they entered the trial; the corresponding survival values for the Polyerga Neu and the placebo groups were 13.9% and 10.1%, respectively. In addition, no differences were found between the three groups with

respect to tumor response, median body weight, blood chemistry values, Karnofsky Performance Status, and QOL. However, more patients in the Iscador group than in the Polyerga Neu or the placebo groups reported subjective improvement in feelings of well-being (59.4% vs. 43.2% and 44.8%, respectively).[26]

Another randomized phase III trial of mistletoe as a treatment for people with cancer involved 830 patients with high-risk melanoma (i.e., a primary tumor >3 mm in diameter and no regional lymph nodes positive for cancer or a primary tumor of any size, one or two regional lymph nodes positive for cancer, and no distant metastases) who were randomly assigned to one of the following four groups after potentially curative surgery:[5]

1. Treatment with low-dose interferon-alpha.
2. Treatment with low-dose interferon-gamma.
3. Treatment with IscadorM.
4. No further treatment.

Both types of interferon and IscadorM were administered by subcutaneous injection for a period of 1 year. The interferon injections were administered every other day, whereas IscadorM was administered 3 times a week for up to 1 year. After 8 years of follow-up, no increase in survival time or increase in time until melanoma recurrence was demonstrated for mistletoe treatment or treatment with either type of interferon.

In another retrospective multicenter cohort study that determined the safety and efficacy of Iscador as an adjuvant long-term treatment after surgery for malignant melanoma, 686 patient records were examined (357 untreated controls and 329 treated with Iscador). Safety, efficacy, and a cluster of survival endpoints (tumor related, disease free, brain metastases free, and OS) were measured. The use of additional adjuvant chemotherapy was more frequent in the Iscador-treated group, while the use of immunotherapy was more frequent in the control group. Only mild to intermediate adverse drug reactions were seen in the treated group. The tumor-related mortality rate was 8.9% in the Iscador group, compared with 10.7% in the control group (P = .017).[27]

Three other studies of mistletoe were described in a single published report.[4] One of the three studies was a large cohort study on the effectiveness of Iscador as a treatment for people with rectal, colon, breast, stomach, or lung cancer.[4] The second and third studies were small, prospective, randomized, matched-pair studies (one randomized, one nonrandomized) that involved patients who were selected from a group of 8,475 individuals who had not been treated with mistletoe.[4]

These studies are summarized in Table 3. The overall conclusion of the authors in the report of these three studies was that Iscador treatment can produce a clinically significant increase in survival in cancer patients. However, there were several weaknesses in the design and execution of these studies. In a large cohort study, the investigators were unable to find matched cohorts for 61% of eligible patients, and even among the patients for whom matches were found, fewer than two-thirds were judged to adhere strictly to the matching criteria; thus, the final analysis contained fewer than 25% of eligible patients. In the two small prospective studies, no records of the amount or duration of Iscador use were kept.

The use of Iscador as an adjuvant treatment has been examined in several studies. In the following studies,

Iscador proved safe and effective and also showed a significant survival advantage over untreated controls.

A retrospective multicenter cohort study of parallel groups examined Iscador as a postoperative adjuvant using safety and efficacy as the main endpoints. A total of 1,442 patient records (710 treated patients and 732 untreated controls) were randomly selected from medical institutions that provided both standard and alternative treatments. Safety and efficacy were measured by the number and severity of adverse drug reactions. The treatment group showed significantly less adverse reactions (confidence interval, 95%; $P <$ .001) compared with the controls.[28,29]

A multicenter, controlled, retrospective observational cohort study that involved nonmetastatic colorectal cancer patients treated between 1993 and 2002 was conducted to evaluate safety and efficacy measures with Iscador. Eight hundred and four consecutive colorectal patients (429 treated with Iscador and 375 controls) from 26 hospitals and practices were included. Iscador was well tolerated, with a significant reduction in adverse events, a higher rate of symptom relief, and improved disease-free survival (DFS) compared with the control group. The study concluded the use of Iscador has a beneficial effect as an adjuvant therapy and long-term treatment for patients with stage I to III colorectal cancer.[30]

A randomized phase II study of Iscador combined with carboplatin-containing regimens was conducted in chemotherapy-naïve patients with advanced non-small cell lung cancer.[31] Seventy-two patients were randomly assigned to receive either chemotherapy alone with carboplatin combined with gemcitabine or pemetrexed (39 patients) or chemotherapy plus Iscador (33 patients) 3 times a week until tumor progression. Time to progression (4.8 months vs. 6 months) and OS (11 months) were similar in both treatment groups. There were no differences in QOL observed between the treatment groups, although chemotherapy dose reductions, nonhematologic toxicities, and hospitalizations were less frequent in patients treated with Iscador in this nonblinded study.

Another U.S. trial (NCT00283478) of the mistletoe extract Iscar with gemcitabine versus gemcitabine alone as a second-line therapy for non-small cell lung cancer patients who have failed one prior line of chemotherapy has been completed but not yet published.

Table 3. Use of Iscador in Cancer Treatment: Clinical Reports Describing Therapeutic Endpoints[a]

Reference	Trial Design	Condition or Cancer Type	Treatment Groups (Enrolled; Treated; Placebo or No Treatment Control)[b]	Results	Concurrent Therapy Used[c]	L Ev S

Reference	Trial Design	Condition or Cancer Type	Treatment Groups (Enrolled; Treated; Placebo or No Treatment Control)[b]	Results	Concurrent Therapy Used[c]	L Ev S
[26]	Randomized trial	Lung, non-small cell, inoperable	408; 105; 107[e]	Subjective improvement in quality of life	Yes[f]	1i
[32]	Randomized trial	Lung, non-small cell, stages I–IV	218; 87; 96	Improved median survival, LN+ patients only	No	1i
[5]	Randomized trial	Melanoma, stages II–III	204; 102; 102	No improvement in DFS or OS rates	No	1i
[24,25]	Randomized trial	Pancreatic, advanced or metastatic	220; 110; 110	Improved OS	No	1i
[33]	Randomized trial	Osteosarcoma, second metastatic relapse	20; 9 (viscum); 11 (etoposide)	Improved DFS compared with etoposide group	No	1i

Reference	Trial Design	Condition or Cancer Type	Treatment Groups (Enrolled; Treated; Placebo or No Treatment Control)[b]	Results	Concurrent Therapy Used[c]	L Ev S
[34]	Randomized trial	Breast	95; 30 (IscadorM) and 34 (HelixorA); 31	No differences in the primary outcome between groups	Yes	1i
[28]	Comparative, retrolective, cohort study	Breast, stages I–IV	1,442; 710; 732	Fewer adverse drug reactions with mistletoe	Yes	2E
[27]	Comparative, retrolective, cohort study	Melanoma, stages II–III	686; 329; 357	Improved overall disease-specific survival	Unknown	2A
[4]	Cohort study	Breast, stage III	8,475[g]; 17[h]; 17[h]	Improved mean survival	Yes	N
[4]	Cohort study	Various types, stages I–IV	8,475[g]; 39[h]; 39[h]	Improved mean survival	Yes	N
[4]	Cohort study	Various types, stages I–IV	10,226[g]; 396[h]; 396[h]	Improved mean survival	Yes	N

Reference	Trial Design	Condition or Cancer Type	Treatment Groups (Enrolled; Treated; Placebo or No Treatment Control)[b]	Results	Concurrent Therapy Used[c]	L Ev S
[30]	Retrospective, observational cohort study	Nonmetastatic colorectal	804; 429; 375	Lower incidence of diarrhea, nausea, loss of appetite, dermatitis, fatigue, and mucositis	Yes	20
[35]	Nonconsecutive case series	Pancreatic	292; 292; various historical controls	Improved median survival	Yes	3i

DFS = disease-free survival; LN+ = lymph node–positive disease; No. = number; OS = overall survival; quality of life.

[a]Refer to text and the NCI Dictionary of Cancer Terms for additional information and definition of te

[b]Number of patients treated plus number of patients controlled may not equal number of patients enrolled; number of patients enrolled = number of patients initially recruited/considered by the researchers who conducted a study; number of patients treated = number of enrolled patients who administered the treatment being studied and for whom results were reported; historical control su are not included in number of patients enrolled.

[c]Chemotherapy, radiation therapy, hormonal therapy, or cytokine therapy administered/allowed at t same time as mistletoe therapy.

[d]For information about levels of evidence analysis and an explanation of the level of evidence score to Levels of Evidence for Human Studies of Integrative, Alternative, and Complementary Therapies.

[e]Control patients were treated with a vitamin B mixture as a placebo; 100 additional evaluable patie were treated with Polyerga Neu, a sheep spleen glycopeptide reported to be an immunostimulant a inhibitor of tumor cell glycolysis; treatment with Polyerga Neu was not found to be beneficial.

Reference	Trial Design	Condition or Cancer Type	Treatment Groups (Enrolled; Treated; Placebo or No Treatment Control)[b]	Results	Concurrent Therapy Used[c]	L Ev S

[f]Radiation therapy for metastases distant from the site of the primary tumor was permitted; radiatio therapy to the primary tumor site or use of other anticancer treatment was not permitted.

[g]Among 10,226 cancer patients enrolled in a retrospective matched-pair, case-control study, 1,751 ha been treated with Iscador or another mistletoe product and 8,475 had not been treated with mistlet from the 8,475 untreated patients, two sets of matched pairs were formed for prospective studies; i prospective studies, one member of each pair was randomly assigned to be treated with Iscador an other member served as a control subject.

[h]Patients were strictly matched according to gender, year of birth ± 3 years, year of diagnosis ± 3 yea type of tumor, stage of disease, and conventional therapy received.

Other Mistletoe Preparations

Studies on Eurixor, Helixor, Lektinol, Isorel, and abnobaVISCUM are summarized in Table 4.

Eurixor

Five randomized controlled trials of Eurixor have been published as peer-reviewed articles. The largest of these studies involved 477 patients with squamous cell carcinoma of the head and neck.[2,15] These patients were randomly assigned to treatment with surgery or surgery and radiation therapy, and they were randomly assigned again to either no additional treatment or treatment with Eurixor. This double randomization produced the following four groups:

1. One hundred five patients treated with surgery alone.
2. Ninety-seven patients treated with surgery and Eurixor.
3. One hundred thirty-seven patients treated with surgery and radiation therapy.
4. One hundred thirty-eight patients treated with surgery, radiation therapy, and Eurixor.

Eurixor was administered in four treatment cycles over a 60-week period. Each treatment cycle lasted 12 weeks and was followed by a 4-week break. During each cycle, Eurixor was administered by subcutaneous injection twice a week. Each injection contained enough standardized mistletoe extract to yield a dose of 1 nanogram of ML-1 lectin per kilogram of body weight. The results of this randomized trial showed that treatment with Eurixor did not improve either 5-year disease-free survival or 5-year disease-specific survival. In addition, no stimulation of the immune system or improvement in QOL was found with Eurixor treatment.

It has been suggested that a less-than-optimum dose of mistletoe was administered to patients in this trial.[4] The same dose of Eurixor, however, has been used in other clinical studies, including studies in which benefit was reported.[1,36] In addition, both the dose and the duration of Eurixor treatment in this trial are consistent with those recommended by the manufacturer.[2]

A prospective, randomized phase II trial involved 45 patients who had noninvasive bladder cancer.[3] After surgery, the patients were randomly assigned to receive either three cycles of treatment with Eurixor or no further therapy. The goal of the study was to determine whether Eurixor treatment could reduce bladder cancer recurrence. Twenty-three patients were randomly assigned to the treatment group, and 22 were randomly assigned to the control group. Each cycle of Eurixor treatment consisted of 3 months of subcutaneous injections, administered twice a week, followed by a 3-month break. One milliliter of Eurixor was administered at each injection. After 18 months of follow-up, 11 recurrences were observed in the treatment group, and 8 were observed in the control group. The average time of recurrence for the treatment group was 6.3 months; for the control group, it was 6.4 months. The median disease-free interval for the treatment group was 9 months; for the control group, it was 10.5 months. None of these differences was considered significant. A major concern about this study, however, is that the dose of lectin ML-1 administered to patients was not adjusted for body weight.

Eurixor is no longer available on the market for sale.

Isorel

Only two trials of Isorel have been reported in the publicly available, online indexed peer-reviewed medical literature. In one study, 64 patients with advanced colorectal cancer (Dukes C and D) were randomly assigned to one of the following three groups:[37]

1. Surgery and chemotherapy.
2. Surgery and chemotherapy plus Isorel.
3. Surgery alone.

Patients receiving treatment with Isorel had a significantly better median survival advantage and a better cumulative survival advantage than patients in the other two groups. In addition there were no side effects to treatment in the Isorel group.

Another study showed that perioperative use of Isorel in patients with cancer of the digestive tract resulted in an increase in lymphocytes through 14 days of drug administration.

Isorel is no longer available on the market for sale.

Helixor

Most studies have been conducted in Europe, primarily in Germany and Austria. One prospective, phase I, dose-escalation trial studied weekly intravenous pine mistletoe aqueous extract given alone. In the 21 patients evaluated, Helixor was well tolerated in doses up to 2,000 mg with mild to moderate fever noted.[38] A subsequent study demonstrated improved median QOL in a group of patients receiving Helixor versus a control group receiving best supportive care.[39]

Other studies have explored the effects of administering Helixor to patients receiving chemotherapy and/or radiation therapy. The National Center for Complementary and Integrative Health in cooperation with the National Cancer Institute (NCI) conducted a phase I trial (NCCAM-02-AT-260) of mistletoe (HelixorA) and gemcitabine in patients with advanced solid tumors. The HelixorA and gemcitabine combination showed limited toxicity, and no botanical-drug interactions were reported.[40] (Also available online.) In a three-arm randomized trial, breast cancer patients were randomly assigned to one of the following groups after surgery: Helixor, chemotherapy, or control. Some patients in each group were also treated with local radiation therapy. The number of evaluable patients in the chemotherapy group was 177, with survival in the chemotherapy group superior to that in the control group and equivalent to that in the Helixor group.[41] The use of Helixor has also been examined in other studies.[39,42-44]

abnobaVISCUM

No tumor response was seen in any of the 25 patients in a phase ll trial that examined the effect of a mistletoe extract, known as abnobaVISCUM, in metastatic colorectal cancer resistant to standard treatment (fluorouracil and leucovorin chemotherapy). The endpoint of the study was objective tumor response. Patients were administered a gradually increasing daily dose of 0.15 mg to 15 mg. Treatment duration ranged from 4 weeks to 66 weeks. Toxicity levels were mild. Some patients reported relief of disease symptoms.[45]

A small, randomized, nonblinded trial of abnobaVISCUM, given postoperatively to 15 patients with resected stage IB or II gastric cancer, showed improved QOL among patients who received the mistletoe extract compared with 16 untreated controls.[46] A small uncontrolled trial of mistletoe plant extract from the same manufacturer (abnobaVISCUM) treated patients with non–muscle-invasive bladder cancer; this trial showed the safety of intravesical administration and had response rates of 56%, which was consistent with the published results of other treatments for bladder cancer (39%–50%).[47]

A single-arm, multicenter, open-label trial evaluated the efficacy and safety of chemical pleurodesis using abnobaVISCUM.[48] Of the 62 patients in the study, 49 patients had a complete response, 11 patients had a partial response, and 2 patients had no response. The observation period was 4 weeks. There are no data on how intrapleural administration compared with standard of care.

Table 4. Use of Other Mistletoe Products in Cancer Treatment: Clinical Reports Describing Therapeutic Endpoints[a]

Reference	Trial Design	Product Tested	Condition or Cancer Type	Treatment Groups (Enrolled; Treated; Placebo or No Treatment Control)[b]	Results

Reference	Trial Design	Product Tested	Condition or Cancer Type	Treatment Groups (Enrolled; Treated; Placebo or No Treatment Control)[b]	Results
[3]	Randomized trial	Eurixor	Bladder, noninvasive	45; 23; 22	DFS did not vary between groups
[1,36]	Randomized trial	Eurixor	Brain, glioma; 74% of patients, stages III–IV; 26% of patients, no stage information	47; 20; 18	Improved survival, stages III–IV patients only
[49,50]	Randomized trial	Eurixor	Colorectal, metastatic	107; 38; 41	Improved QOL
[2]	Randomized trial	Eurixor	Head and neck, squamous cell, stages I–IV	495; 235[e]; 242[e]	No differences in DFS between groups
[41]	Randomized trial	Helixor	Breast, stages I–III	692; 192 (Helixor) and 177 (chemotherapy); 274	Improved survival
[51]	Randomized trial	Helixor	Colorectal, metastatic	60; 20; 20	Improved mean survival

Reference	Trial Design	Product Tested	Condition or Cancer Type	Treatment Groups (Enrolled; Treated; Placebo or No Treatment Control)[b]	Results
[39]	Randomized trial	Helixor	Breast, ovarian, and non-small cell lung	224; 115; 109	Improved QOL
[34]	Randomized trial	HelixorA, IscadorM	Breast	95; 34 (HelixorA) and 30 (IscadorM); 31	No differences in the primary outcome between groups
[13]	Randomized controlled trial	PS76A (Lektin)	Breast	352; 176; 176	Improved QOL
[52]	Randomized trial	Lektinol	Breast	261; 195; 66	Improved QOL
[53]	Randomized trial	Lektinol	Breast	352; 176; 176	Improved QOL
[37]	Randomized trial	Isorel	Colorectal	64; 50; 14	Improved survival and tolerance to either adjuvant or palliative treatment

Reference	Trial Design	Product Tested	Condition or Cancer Type	Treatment Groups (Enrolled; Treated; Placebo or No Treatment Control)[b]	Results
[54]	Nonrandomized controlled trial	Isorel	Digestive tract	70; 40; 30	Enhanced cellular immunity and improved QOL
[45]	Nonrandomized controlled trial	abnobaVISCUM *Quercus*	Metastatic colorectal	25; 25; none	No objective tumor response
[21]	Nonrandomized controlled trial	Viscum fraxini-2	Hepatocellular carcinoma	23; 23; none	Improved survival

DFS = disease-free survival; No. = number; QOL = quality of life.

[a]Refer to text and the NCI Dictionary of Cancer Terms for additional information and definition of te

[b]Number of patients treated plus number of patients controlled may not equal number of patients e patients enrolled = number of patients initially recruited/considered by the researchers who conduc patients treated = number of enrolled patients who were administered the treatment being studied were reported; historical control subjects are not included in number of patients enrolled.

[c]Chemotherapy, radiation therapy, hormonal therapy, or cytokine therapy administered/allowed at t therapy.

[d]For information about levels of evidence analysis and an explanation of the level of evidence score Evidence for Human Studies of Integrative, Alternative, and Complementary Therapies.

[e]This was a four-arm trial; patients were randomly assigned to surgery only or to surgery plus radiati second randomization to no mistletoe treatment or to treatment with Eurixor; the resulting treatme following numbers of evaluable patients: surgery only = 105, surgery plus Eurixor = 97, surgery plus r surgery plus radiation therapy plus Eurixor = 138; radiation therapy and Eurixor treatment overlapped was superior in terms of disease-free survival, disease-specific survival, improvement in QOL, or stir

Reference	Trial Design	Product Tested	Condition or Cancer Type	Treatment Groups (Enrolled; Treated; Placebo or No Treatment Control)[b]	Results

system; in the table, mistletoe-treated and nontreated (control) patients were grouped (i.e., numbe and number control = 105 + 137 = 242).

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

References

1. Lenartz D, Dott U, Menzel J, et al.: Survival of glioma patients after complementary treatment with galactoside-specific lectin from mistletoe. Anticancer Res 20 (3B): 2073-6, 2000 May-Jun. [PUBMED Abstract]
2. Steuer-Vogt MK, Bonkowsky V, Ambrosch P, et al.: The effect of an adjuvant mistletoe treatment programme in resected head and neck cancer patients: a randomised controlled clinical trial. Eur J Cancer 37 (1): 23-31, 2001. [PUBMED Abstract]
3. Goebell PJ, Otto T, Suhr J, et al.: Evaluation of an unconventional treatment modality with mistletoe lectin to prevent recurrence of superficial bladder cancer: a randomized phase II trial. J Urol 168 (1): 72-5, 2002. [PUBMED Abstract]
4. Grossarth-Maticek R, Kiene H, Baumgartner SM, et al.: Use of Iscador, an extract of European mistletoe (Viscum album), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. Altern Ther Health Med 7 (3): 57-66, 68-72, 74-6 passim, 2001 May-Jun. [PUBMED Abstract]
5. Kleeberg UR, Suciu S, Bröcker EB, et al.: Final results of the EORTC 18871/DKG 80-1 randomised phase III trial. rIFN-alpha2b versus rIFN-gamma versus ISCADOR M versus observation after surgery in melanoma patients with either high-risk primary (thickness >3 mm) or regional lymph node metastasis. Eur J Cancer 40 (3): 390-402, 2004. [PUBMED Abstract]
6. Viscum album. In: Homoeopathic Pharmacopoeia Convention of the United States: Homoeopathic Pharmacopoeia of the United States. 2002, Monograph 9444 Visc.
7. Tröger W, Jezdić S, Ždrale Z, et al.: Quality of life and neutropenia in patients with early stage breast cancer: a randomized pilot study comparing additional treatment with mistletoe extract to chemotherapy alone . Breast Cancer: Basic and Clinical Research 3: 35-45, 2009.
8. Grossarth-Maticek R, Ziegler R: Prospective controlled cohort studies on long-term therapy of breast cancer patients with a mistletoe preparation (Iscador). Forsch Komplementmed 13 (5): 285-92, 2006. [PUBMED Abstract]

9. Grossarth-Maticek R, Ziegler R: Prospective controlled cohort studies on long-term therapy of cervical cancer patients with a mistletoe preparation (Iscador). Forsch Komplementmed 14 (3): 140-7, 2007. [PUBMED Abstract]

10. Grossarth-Maticek R, Ziegler R: Randomized and non-randomized prospective controlled cohort studies in matched pair design for the long-term therapy of corpus uteri cancer patients with a mistletoe preparation (Iscador). Eur J Med Res 13 (3): 107-20, 2008. [PUBMED Abstract]

11. Grossarth-Maticek R, Ziegler R: Prospective controlled cohort studies on long-term therapy of ovairian cancer patients with mistletoe (Viscum album L.) extracts iscador. Arzneimittelforschung 57 (10): 665-78, 2007. [PUBMED Abstract]

12. Bar-Sela G, Goldberg H, Beck D, et al.: Reducing malignant ascites accumulation by repeated intraperitoneal administrations of a Viscum album extract. Anticancer Res 26 (1B): 709-13, 2006 Jan-Feb. [PUBMED Abstract]

13. Wetzel D, Schäfer M: Results of a randomised placebo-controlled multicentre study with PS76A2 (standardised mistletoe preparation) in patients with breast cancer receiving adjuvant chemotherapy. [Abstract] Phytomedicine 7 (Suppl 2): A-SL-66, 2000.

14. Schöffski P, Riggert S, Fumoleau P, et al.: Phase I trial of intravenous aviscumine (rViscumin) in patients with solid tumors: a study of the European Organization for Research and Treatment of Cancer New Drug Development Group. Ann Oncol 15 (12): 1816-24, 2004. [PUBMED Abstract]

15. Stauder H, Kreuser ED: Mistletoe extracts standardised in terms of mistletoe lectins (ML I) in oncology: current state of clinical research. Onkologie 25 (4): 374-80, 2002. [PUBMED Abstract]

16. Kienle GS, Berrino F, Büssing A, et al.: Mistletoe in cancer - a systematic review on controlled clinical trials. Eur J Med Res 8 (3): 109-19, 2003. [PUBMED Abstract]

17. Kienle GS, Glockmann A, Schink M, et al.: Viscum album L. extracts in breast and gynaecological cancers: a systematic review of clinical and preclinical research. J Exp Clin Cancer Res 28: 79, 2009. [PUBMED Abstract]

18. Horneber MA, Bueschel G, Huber R, et al.: Mistletoe therapy in oncology. Cochrane Database Syst Rev (2): CD003297, 2008. [PUBMED Abstract]

19. Kienle GS, Kiene H: Complementary cancer therapy: a systematic review of prospective clinical trials on anthroposophic mistletoe extracts. Eur J Med Res 12 (3): 103-19, 2007. [PUBMED Abstract]

20. Ernst E, Schmidt K, Steuer-Vogt MK: Mistletoe for cancer? A systematic review of randomised clinical trials. Int J Cancer 107 (2): 262-7, 2003. [PUBMED Abstract]

21. Mabed M, El-Helw L, Shamaa S: Phase II study of viscum fraxini-2 in patients with advanced hepatocellular carcinoma. Br J Cancer 90 (1): 65-9, 2004. [PUBMED Abstract]

22. Kienle GS, Kiene H: Review article: Influence of Viscum album L (European mistletoe) extracts on quality of life in cancer patients: a systematic review of controlled clinical studies. Integr Cancer Ther 9 (2): 142-57, 2010. [PUBMED Abstract]

23. Oei SL, Thronicke A, Kröz M, et al.: Impact of Oncological Therapy and Viscum album L Treatment on Cancer-Related Fatigue and Internal Coherence in Nonmetastasized Breast Cancer Patients. Integr Cancer Ther 19: 1534735420917211, 2020 Jan-Dec. [PUBMED Abstract]

24. Tröger W, Galun D, Reif M, et al.: Viscum album [L.] extract therapy in patients with locally advanced or

metastatic pancreatic cancer: a randomised clinical trial on overall survival. Eur J Cancer 49 (18): 3788-97, 2013. [PUBMED Abstract]

25. Tröger W, Galun D, Reif M, et al.: Quality of life of patients with advanced pancreatic cancer during treatment with mistletoe: a randomized controlled trial. Dtsch Arztebl Int 111 (29-30): 493-502, 33 p following 502, 2014. [PUBMED Abstract]
26. Dold U, Edler L, Mäurer HCh, et al., eds.: [Adjuvant Cancer Therapy in Advanced Non-Small Cell Bronchial Cancer: Multicentric Controlled Studies To Test the Efficacy of Iscador and Polyerga]. Georg Thieme Verlag, 1991.
27. Augustin M, Bock PR, Hanisch J, et al.: Safety and efficacy of the long-term adjuvant treatment of primary intermediate- to high-risk malignant melanoma (UICC/AJCC stage II and III) with a standardized fermented European mistletoe (Viscum album L.) extract. Results from a multicenter, comparative, epidemiological cohort study in Germany and Switzerland. Arzneimittelforschung 55 (1): 38-49, 2005. [PUBMED Abstract]
28. Bock PR, Friedel WE, Hanisch J, et al.: Retrolective, comparative, epidemiological cohort study with parallel groups design for evaluation of efficacy and safety of drugs with "well-established use". Forsch Komplementarmed Klass Naturheilkd 11 (Suppl 1): 23-9, 2004. [PUBMED Abstract]
29. Bock PR, Friedel WE, Hanisch J, et al.: [Efficacy and safety of long-term complementary treatment with standardized European mistletoe extract (Viscum album L.) in addition to the conventional adjuvant oncologic therapy in patients with primary non-metastasized mammary carcinoma. Results of a multi-center, comparative, epidemiological cohort study in Germany and Switzerland] Arzneimittelforschung 54 (8): 456-66, 2004. [PUBMED Abstract]
30. Friedel WE, Matthes H, Bock PR, et al.: Systematic evaluation of the clinical effects of supportive mistletoe treatment within chemo- and/or radiotherapy protocols and long-term mistletoe application in nonmetastatic colorectal carcinoma: multicenter, controlled, observational cohort study. J Soc Integr Oncol 7 (4): 137-45, 2009. [PUBMED Abstract]
31. Bar-Sela G, Wollner M, Hammer L, et al.: Mistletoe as complementary treatment in patients with advanced non-small-cell lung cancer treated with carboplatin-based combinations: a randomised phase II study. Eur J Cancer 49 (5): 1058-64, 2013. [PUBMED Abstract]
32. Salzer G, Danmayr E, Wutzholfer F, et al.: [Adjuvant Iscador® treatment of non-small cell bronchial carcinoma. Results of a randomized study]. Dtsch Z Onkol 23 (4): 93-8, 1991.
33. Longhi A, Reif M, Mariani E, et al.: A Randomized Study on Postrelapse Disease-Free Survival with Adjuvant Mistletoe versus Oral Etoposide in Osteosarcoma Patients. Evid Based Complement Alternat Med 2014: 210198, 2014. [PUBMED Abstract]
34. Pelzer F, Tröger W, Nat DR: Complementary Treatment with Mistletoe Extracts During Chemotherapy: Safety, Neutropenia, Fever, and Quality of Life Assessed in a Randomized Study. J Altern Complement Med 24 (9-10): 954-961, 2018 Sep/Oct. [PUBMED Abstract]
35. Schaefermeyer G, Schaefermeyer H: Treatment of pancreatic cancer with Viscum album (Iscador): a retrospective study of 292 patients 1986-1996. Complement Ther Med 6 (4): 172-7, 1998.
36. Lenartz D, Stoffel B, Menzel J, et al.: Immunoprotective activity of the galactoside-specific lectin from mistletoe after tumor destructive therapy in glioma patients. Anticancer Res 16 (6B): 3799-802, 1996 Nov-Dec. [PUBMED Abstract]

37. Cazacu M, Oniu T, Lungoci C, et al.: The influence of isorel on the advanced colorectal cancer. Cancer Biother Radiopharm 18 (1): 27-34, 2003. [PUBMED Abstract]

38. Huber R, Schlodder D, Effertz C, et al.: Safety of intravenously applied mistletoe extract - results from a phase I dose escalation study in patients with advanced cancer. BMC Complement Altern Med 17 (1): 465, 2017. [PUBMED Abstract]

39. Piao BK, Wang YX, Xie GR, et al.: Impact of complementary mistletoe extract treatment on quality of life in breast, ovarian and non-small cell lung cancer patients. A prospective randomized controlled clinical trial. Anticancer Res 24 (1): 303-9, 2004 Jan-Feb. [PUBMED Abstract]

40. Mansky PJ, Wallerstedt DB, Sannes TS, et al.: NCCAM/NCI Phase 1 Study of Mistletoe Extract and Gemcitabine in Patients with Advanced Solid Tumors. Evid Based Complement Alternat Med 2013: 964592, 2013. [PUBMED Abstract]

41. Gutsch J, Berger H, Scholz G, et al.: [Prospective study in radically operated breast cancer with polychemotherapy, Helixor® and untreated controls]. Dtsch Z Onkol 21: 94-101, 1988.

42. Auerbach L, Dostal V, Václavik-Fleck I, et al.: Signifikant höherer anteil aktivierter NK-Zellen durch additive misteltherapie bei chemotherapierten mamma-Ca-patientinnen in einer prospektiven randomisierten doppelblinden studie. In: Scheer R, Bauer R, Becker H, et al.: Fortschritte in der Misteltherapie. Aktueller Stand der Forschung und klinischen Anwendung. KCV-Verlag, 2005, pp 543-54.

43. Matthes HF, Schad F, Buchwald D, et al.: Endoscopic ultrasound-guided fine-needle Injection of Viscum album L. (mistletoe; Helixor M) in the therapy of primary inoperable pancreas cancer: a pilot study. [Abstract] Gastroenterology 128 (Suppl 2): A-T988, A433-A434, 2005.

44. Beuth J, Schneider B, Schierholz JM: Impact of complementary treatment of breast cancer patients with standardized mistletoe extract during aftercare: a controlled multicenter comparative epidemiological cohort study. Anticancer Res 28 (1B): 523-7, 2008 Jan-Feb. [PUBMED Abstract]

45. Bar-Sela G, Haim N: Abnoba-viscum (mistletoe extract) in metastatic colorectal carcinoma resistant to 5-fluorouracil and leucovorin-based chemotherapy. Med Oncol 21 (3): 251-4, 2004. [PUBMED Abstract]

46. Kim KC, Yook JH, Eisenbraun J, et al.: Quality of life, immunomodulation and safety of adjuvant mistletoe treatment in patients with gastric carcinoma - a randomized, controlled pilot study. BMC Complement Altern Med 12: 172, 2012. [PUBMED Abstract]

47. 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. J Urol 194 (4): 939-43, 2015. [PUBMED Abstract]

48. Cho JS, Na KJ, Lee Y, et al.: Chemical Pleurodesis Using Mistletoe Extraction (ABNOVAviscum(®) Injection) for Malignant Pleural Effusion. Ann Thorac Cardiovasc Surg 22 (1): 20-6, 2016. [PUBMED Abstract]

49. Heiny BM, Albrecht V, Beuth J: Stabilization of quality of life with mistletoe lectin-1-standardized extract in advanced colorectal carcinoma. Onkologe 4 (Suppl 1): S35-9, 1998.

50. Sauer H: Quality of life stabilization with mistletoe-1-standardized extract in advanced colorectal carcinoma [Letter]. Onkologe 4: 1180, 1998.

51. Douwes FR, Wolfrum DI, Migeod F: [Results of a prospective randomized study: chemotherapy versus chemotherapy plus "biological response modifier" in metastasizing colorectal carcinoma]. Dtsch Z Onkol 18 (6): 155-64, 1986.

52. Semiglasov VF, Stepula VV, Dudov A, et al.: The standardised mistletoe extract PS76A2 improves QoL in patients with breast cancer receiving adjuvant CMF chemotherapy: a randomised, placebo-controlled, double-blind, multicentre clinical trial. Anticancer Res 24 (2C): 1293-302, 2004 Mar-Apr. [PUBMED Abstract]

53. Semiglazov VF, Stepula VV, Dudov A, et al.: Quality of life is improved in breast cancer patients by Standardised Mistletoe Extract PS76A2 during chemotherapy and follow-up: a randomised, placebo-controlled, double-blind, multicentre clinical trial. Anticancer Res 26 (2B): 1519-29, 2006 Mar-Apr. [PUBMED Abstract]

54. Enesel MB, Acalovschi I, Grosu V, et al.: Perioperative application of the Viscum album extract Isorel in digestive tract cancer patients. Anticancer Res 25 (6C): 4583-90, 2005 Nov-Dec. [PUBMED Abstract]

Adverse Effects

Although a number of different mistletoe extracts have been used in human studies, the reported side effects have generally been minimal and not life threatening. Common side effects include the following:[1-4]

- Soreness and inflammation at injection sites.
- Headache.
- Fever.
- Chills.

One meta-analysis using *Viscum album L.* and isolated mistletoe lectins included both animal and human studies. Doses and application forms varied. No immunosuppressive effects were reported. Side effects included local reactions at the injection site and flu-like symptoms such as fever, chills, fatigue, mild gastrointestinal symptoms, and headache. High doses of recombinantly-produced mistletoe lectins (not available in commercial products) resulted in reversible hepatotoxicity in some cases.[5] Another review reported adverse reactions that included local reactions at the injection site, fever, increased intracerebral pressure, headache, circulatory problems, thrombophlebitis, swelling of lymph nodes, and allergic reactions.[6]

A few cases of severe allergic reactions, including anaphylactic shock, have been reported.[2]

Although from an observational cohort study, three types of mistletoe (Iscador, Helixor, and abnobaVISCUM) that were given intratumorally, intravenously, or subcutaneously were found to be safe in a small group of cancer patients with autoimmune diseases such as Graves disease, Hashimoto thyroiditis, ulcerative colitis, psoriasis, and some rheumatic diseases.[7]

References

1. Kaegi E: Unconventional therapies for cancer: 3. Iscador. Task Force on Alternative Therapies of the Canadian Breast Cancer Research Initiative. CMAJ 158 (9): 1157-9, 1998. [PUBMED Abstract]

2. Hutt N, Kopferschmitt-Kubler M, Cabalion J, et al.: Anaphylactic reactions after therapeutic injection of mistletoe (Viscum album L.). Allergol Immunopathol (Madr) 29 (5): 201-3, 2001 Sep-Oct. [PUBMED

Abstract]

3. Stauder H, Kreuser ED: Mistletoe extracts standardised in terms of mistletoe lectins (ML I) in oncology: current state of clinical research. Onkologie 25 (4): 374-80, 2002. [PUBMED Abstract]
4. Steele ML, Axtner J, Happe A, et al.: Safety of Intravenous Application of Mistletoe (Viscum album L.) Preparations in Oncology: An Observational Study. Evid Based Complement Alternat Med 2014: 236310, 2014. [PUBMED Abstract]
5. Kienle GS, Grugel R, Kiene H: Safety of higher dosages of Viscum album L. in animals and humans--systematic review of immune changes and safety parameters. BMC Complement Altern Med 11: 72, 2011. [PUBMED Abstract]
6. Ernst E, Schmidt K, Steuer-Vogt MK: Mistletoe for cancer? A systematic review of randomised clinical trials. Int J Cancer 107 (2): 262-7, 2003. [PUBMED Abstract]
7. Oei SL, Thronicke A, Kröz M, et al.: Use and Safety of Viscum album L Applications in Cancer Patients With Preexisting Autoimmune Diseases: Findings From the Network Oncology Study. Integr Cancer Ther 18: 1534735419832367, 2019 Jan-Dec. [PUBMED Abstract]

Summary of the Evidence for Mistletoe Extracts

Mistletoe is one of the most widely studied complementary and alternative medicine therapies for cancer. In certain European countries, the preparations made from European mistletoe (*Viscum album* L.) are among the most prescribed drugs offered to cancer patients. Mistletoe extracts have been evaluated in numerous clinical studies and improvements in survival, quality of life, and/or stimulation of the immune system have been frequently reported. However, most clinical studies conducted have had one or more major weaknesses that raise doubts about the reliability of the findings. In addition, no evidence exists to support the notion that stimulation of the immune system by mistletoe leads to an improved ability to fight cancer. Because all patients in the reported clinical studies appear to have been adults, no information is available about the use of mistletoe as a treatment for children with cancer.

Separate levels of evidence scores are assigned to qualifying human studies on the basis of statistical strength of the study design and scientific strength of the treatment outcomes (i.e., endpoints) measured. The resulting two scores are then combined to produce an overall score. For additional information about levels of evidence analysis, refer to Levels of Evidence for Human Studies of Integrative, Alternative, and Complementary Therapies.

Changes to This Summary (03/17/2021)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Human/Clinical Studies

Revised text to state that most studies reported an improvement in quality of life, as did a noncontrolled, nonrandomized, real-world study that analyzed patient registry data (cited Oei et al. as reference 23).

This summary is written and maintained by the PDQ Integrative, Alternative, and Complementary Therapies Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ® - NCI's Comprehensive Cancer Database pages.

About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the use of mistletoe extracts in the treatment of people with cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates

This summary is reviewed regularly and updated as necessary by the PDQ Integrative, Alternative, and Complementary Therapies Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Board members review recently published articles each month to determine whether an article should:

- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

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Levels of Evidence

Some of the reference citations in this summary are accompanied by a level-of-evidence designation. These designations are intended to help readers assess the strength of the evidence supporting the use of specific interventions or approaches. The PDQ Integrative, Alternative, and Complementary Therapies Editorial Board uses a formal evidence ranking system in developing its level-of-evidence designations.

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The preferred citation for this PDQ summary is:

PDQ® Integrative, Alternative, and Complementary Therapies Editorial Board. PDQ Mistletoe Extracts. Bethesda, MD: National Cancer Institute. Updated <MM/DD/YYYY>. Available at: https://www.cancer.gov/about-cancer/treatment/cam/hp/mistletoe-pdq. Accessed <MM/DD/YYYY>. [PMID: 26389489]

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