

Mistletoe therapy and cancer; an overview 2017

Mistletoe extracts (*Viscum album* L., VAE) are widely used integrative cancer care treatments, particularly in Europe [1-5]. They are an old herbal remedy [6, 7] and were introduced as cancer treatment in 1920 by Rudolf Steiner and Ita Wegman, founders of Anthroposophic Medicine [8]. *Viscum album* is a hemiparasitic shrub, growing on different host trees. Different preparations are available for the treatment of cancer (currently Abnobaviscum®, Helixor®, Iscador®, Iscucin® and Lektinol®). They are available from different host trees such as oak, apple, pine and many others. They are applied parenteral, particularly subcutaneous, but also intravenous, intratumoural, intrapleural, intraperitoneal and other sites.

Several pharmacologically active compounds have been isolated from VAE, such as mistletoe lectins (ML I, II and III) [9], viscotoxins [10, 11], oligo- and polysaccharides [12, 13], lipophilic extracts [14] and various others [6, 7]. Currently VAE triterpenes are gaining great interest. [15-19] The most prominent properties of VAE are their cytotoxic and growth-inhibiting effects, in vitro, on a variety of human tumour cell lines, lymphocytes and fibroblasts [6, 7]. The cytotoxic effects of VAE are mainly due to the apoptosis-inducing mistletoe lectins [20-22], while the viscotoxins induce necrotic cell death [21, 23]. VAE are also recognized for their immune-modulating activity: In vitro and in vivo studies have demonstrated activation of monocytes/macrophages, granulocytes, natural killer (NK) cells, NK-cell mediated tumor cell lysis, T-cells (especially T-helper-cells) and the induction of various cytokines [6, 7, 24]. VAE also downregulate tumor genes, reduce motility and invasiveness of tumor cells [24], and show antiangiogenic effects [25]. They also possess DNA stabilizing properties, they reduce chromosome damage and improve DNA repair [26-29]. In animals, VAE displays potent antitumour effects when administered either directly into the tumour or systemically [6, 7, 30].

Clinical effectiveness of mistletoe extracts in cancer has been investigated in a great number of studies, among these 43 prospective randomized controlled trials [31-80]: They predominantly report significant clinical benefits. With regard to quality of studies and consistency of results, the best evidence concerning efficacy of mistletoe therapy exists for the improvement of quality of life, increase of weight, and improved tolerability of cytoreductive therapies (chemotherapy, radiotherapy, surgery) [33, 81, 82]. Regarding survival, a well-designed randomized controlled trial has recently shown a highly significant benefit in advanced pancreatic cancer [32]. Other studies showed similar results [30, 83-85]. Effectiveness seems to depend on the duration of the mistletoe therapy, in addition to factors relating to dosage, host tree and choice of preparation. Tumour remissions have been repeatedly observed after local application of high dose mistletoe extracts. This finding is consistent with the preclinical research on cytotoxicity and treatment of tumors in animals. During customary low-dose mistletoe therapy, tumour remissions are rare exceptions. Tumor remissions have therefore been reported primarily in small studies, case series and single cases. (e.g. [30, 84, 86-96])

According to highly experienced practitioners much improved outcomes are possible, with highly individualized and comprehensive treatment schedules – individually adjusted and with selected dosage, preparation, host tree, injection site, time schedule of administration, and supplementation with other interventions. This still needs to be investigated. [97, 98]

Currently, several interesting trials have been started: One large publicly funded confirmative (phase III) randomized controlled trial investigating the influence of mistletoe treatment on survival and health-related quality of life in patients with advanced pancreatic cancer, conducted at several cancer centers in Sweden

(NCT02948309). One phase I trial on safety of intravenous mistletoe infusions in various cancers, conducted at the John Hopkins Hospital in Baltimore (NCT03051477 [99]), funded by the charity organization Believe Big (www.believebig.org). And one large confirmative (phase III) randomized controlled on the efficacy and safety of intravesical mistletoe extract compared to Mitomycin instillation in superficial bladder cancer, conducted in more than 30 German study sites. [100]

Clinical application of mistletoe extracts is safe, even in high dosages [6, 7, 101-106].

March 2017

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Enclosed, exemplary literature:

1. Tröger W, Galun D, Reif M, Schumann A, Stankovic N, Milicevic M: **Quality of life of patients with advanced pancreatic cancer during treatment with mistletoe—a randomized controlled trial.** *Dtsch Arztebl Int* 2014, **111**:493-502
<http://www.aerzteblatt.de/pdf.asp?id=161151>
2. Tröger W, Galun D, Reif M, Schumann A, Stankovic N, Milicevic M: **Viscum album [L.] extract therapy in patients with locally advanced or metastatic pancreatic cancer: a randomised clinical trial on overall survival.** *Eur J Cancer* 2013, **49**:3788-3797
<http://www.ejancer.com/article/S0959-8049%2813%2900550-9/pdf>
3. Mansky PJ, Wallerstedt DB, Sannes TS, Stagl J, Johnson LL, Blackman MR, Grem JL, Swain SM, Monahan BP: **NCCAM/NCI Phase 1 Study of Mistletoe Extract and Gemcitabine in Patients with Advanced Solid Tumors.** *Evidence-Based Complementary and Alternative Medicine* 2013, **2013**: 964592
<http://www.hindawi.com/journals/ecam/2013/964592/>
4. Mamed M, El-Helw L, Sharma S: **Phase II study of viscum fraxini-2 in patients with advanced hepatocellular carcinoma.** *Br J Cancer* 2004, **90**:65-69
<http://www.nature.com/bjc/journal/v90/n1/full/6601463a.html>
5. Piao BK, Wang YX, Xie GR, Mansmann U, Matthes H, Beuth J, Lin HS: **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* 2004, **24**:303-309
<http://ar.iijournals.org/content/24/1/303.full.pdf>
6. Semiglasov VF, Stepula VV, Dudov A, Schnitker J, Mengs U: **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* 2006, **26**:1519-1530
<http://ar.iijournals.org/content/26/2B/1519.full.pdf>
7. Kienle GS, Grugel R, Kienle 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* 2011, **11**:72
<http://www.biomedcentral.com/content/pdf/1472-6882-11-72.pdf>
8. Kienle GS, Glockmann A, Schink M, Kienle H: **Viscum album L. extracts in breast and gynaecological cancers: a systematic review of clinical and preclinical research.** *Journal of Experimental & Clinical Cancer Research: CR* 2009, **28**:79
<http://www.biomedcentral.com/content/pdf/1756-9966-28-79.pdf>
9. Kienle GS, Kienle H: **Complementary cancer therapy: a systematic review of prospective clinical trials on anthroposophic mistletoe extracts.** *Eur J Med Res* 2007, **12**:103-119
http://www.daig-net.de/site-content/die-daig/fachorgan/2007-1/ejomr-2007_3-pdfs/S.103_Kienle.pdf
10. Kienle GS, Kienle H: **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* 2010, **9**:142-157
<http://ict.sagepub.com/content/9/2/142.long>

Reference List

1. Molassiotis A, Fernandez-Ortega P, Pud D, Ozden G, Scott JA, Panteli V, Margulies A, Browall M, Magri M, Selvekerova S: **Use of complementary and alternative medicine in cancer patients: a European survey.** *Ann Oncol* 2005, **16**(4):655.
2. Weis J, Bartsch HH, Hennies F, Rietschel M, Heim M, Adam G, Gartner U, Ammon A: **Complementary medicine in cancer patients: demand, patients' attitudes and psychological beliefs.** *Onkologie* 1998, **21**:144-149.
3. Petru E, Schmied P, Petru C: **Komplementäre Maßnahmen bei Patientinnen mit gynäkologischen Malignomen unter Chemo- und Hormontherapie - Bestandsaufnahme und kritische Überlegungen für die Praxis.** *Geburtshilfe Frauenheilkd* 2001, **61**:75-78.
4. Längler A, Spix C, Seifert G, Gottschling S, Graf N, Kaatsch P: **Complementary and alternative treatment methods in children with cancer: A population-based retrospective survey on the prevalence of use in Germany.** *Eur J Cancer* 2008, **44**(15):2233-2240.
5. Fasching PA, Thiel F, Nicolaisen-Murmann K, Rau H, Engel J, Lux MP, Beckmann MW, Bani MR: **Association of complementary methods with quality of life and life satisfaction in patients with gynecologic and breast malignancies.** *Support Care Cancer* 2007, **55**(11):1277-1284.
6. Kienle GS, Kiene H: **Die Mistel in der Onkologie - Fakten und konzeptionelle Grundlagen.** Stuttgart, New York: Schattauer Verlag; 2003.
7. Büssing A: **Mistletoe. The Genus Viscum** Amsterdam: Hardwood Academic Publishers; 2000.
8. Kienle GS, Kiene H, Albonico HU: **Anthroposophic Medicine: Effectiveness, Utility, Costs, Safety.** Stuttgart, New York: Schattauer Verlag; 2006.
9. Franz H, Ziska P, Kindt A: **Isolation and properties of three lectins from mistletoe (Viscum album L.).** *Biochemical Journal* 1981, **195**:481-484.
10. Winterfeld K, Bijnen AB: **Viscotoxin, ein neuer Inhaltsstoff der Mistel (Viscum album L.).** *Liebigs Ann Chem* 1948, **561**:107-115.
11. Winterfeld K, Kronenthaler A: **Zur Chemie des blutdrucksenkenden Bestandteils der Mistel. (Viscum album).** *Arch Pharm* 1942, **280**:103-115.
12. Mueller EA, Anderer FA: **A Viscum album oligosaccharide activating human natural cytotoxicity is an interferon gamma inducer.** *Cancer Immunol Immunother* 1990, **32**:221-227.
13. Klett CY, Anderer FA: **Activation of natural killer cell cytotoxicity of human blood monocytes by a low molecular weight component from Viscum album extract.** *Arzneimittel-Forschung/Drug Research* 1989, **39** (II)(12):1580-1585.
14. Urech K, Scher JM, Hostanska K, Becker H: **Apoptosis inducing activity of viscin, a lipophilic extract from Viscum album L.** *Journal of Pharmacy and Pharmacology* 2005, **57** 101-109.
15. Struh CM, Jager S, Kersten A, Schempp CM, Scheffler A, Martin SF: **Triterpenoids amplify antitumoral effects of mistletoe extracts on murine B16.f10 melanoma in vivo.** *PLoS One* 2013, **8**(4):e62168.
16. Struh CM, Jager S, Schempp CM, Scheffler A, Martin SF: **A novel triterpene extract from mistletoe induces rapid apoptosis in murine B16.F10 melanoma cells.** *Phytother Res* 2012, **26**(10):1507-1512.
17. Delebinski CI, Jaeger S, Kemnitz-Hassanin K, Henze G, Lode HN, Seifert GJ: **A new development of triterpene acid-containing extracts from Viscum album L. displays synergistic induction of apoptosis in acute lymphoblastic leukaemia.** *Cell Prolif* 2012, **45**(2):176-187.
18. Kleinsimon S, Kauczor G, Jaeger S, Eggert A, Seifert G, Delebinski C: **ViscumTT induces apoptosis and alters IAP expression in osteosarcoma in vitro and has synergistic action when combined with different chemotherapeutic drugs.** *BMC Complement Altern Med* 2017, **17**(1):26.
19. Twardziok M, Kleinsimon S, Rolff J, Jager S, Eggert A, Seifert G, Delebinski CI: **Multiple Active Compounds from Viscum album L. Synergistically Converge to Promote Apoptosis in Ewing Sarcoma.** *PLoS One* 2016, **11**(9):e0159749.
20. Büssing A: **Induction of apoptosis by the mistletoe lectins: a review on the mechanisms of cytotoxicity mediated by Viscum album L.** *Apoptosis* 1996(1):25-32.
21. Büssing A, Verweken W, Wagner M, Wagner B, Pföller U, Schietzel M: **Expression of mitochondrial Apo2.7 molecules and Caspase-3 activation in human lymphocytes treated with the ribosomeinhibiting mistletoe lectins and the cell membrane permeabilizing viscotoxins.** *Cytometry* 1999, **37**(2):133-139.
22. 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).** *Arzneimittel-Forschung/Drug Research* 1993, **43**(II)(11):1221-1227.
23. Büssing A, Schaller G, Pföller U: **Generation of reactive oxygen intermediates (ROI) by the thionins from Viscum album L.** *Anticancer Res* 1998, **18**:4291-4296.

24. Podlech O, Harter PN, Mittelbronn M, Poschel S, Naumann U: **Fermented mistletoe extract as a multimodal antitumoral agent in gliomas.** *Evid Based Complement Alternat Med* 2012, **2012**:501796.
25. Elluru SR, Van Huyen JPD, Delignat S, Prost F, Heudes D, Kazatchkine MD, Friboulet A, Kaveri SV: **Antiangiogenic properties of Viscum album extracts are associated with endothelial cytotoxicity.** *Anticancer Res* 2009, **29**(8):2945.
26. Büssing A, Azhari T, Ostendorp K, Lehnert A, Schweizer K: **Viscum album L. extracts reduce sister chromatid exchanges in cultured peripheral blood mononuclear cells.** *Eur J Cancer* 1994, **30A**(12):1836-1841.
27. Büssing A, Jungmann H, Suzart K, Schweizer K: **Suppression of sister chromatid exchange-inducing DNA lesions in cultured peripheral blood mononuclear cells by Viscum album L.** *J Exp Clin Cancer Res* 1996, **15**:107-114.
28. 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 Letters* 1995(94):199-205.
29. Kovacs E, Hajto T, Hostanska K: **Improvement of DNA repair in lymphocytes of breast cancer patients treated with Viscum album extract (Iscador).** *Eur J Cancer* 1991, **27**(12):1672-1676.
30. Kienle GS, Glockmann A, Schink M, Kiene H: **Viscum album L. extracts in breast and gynaecologic cancers: A systematic review of clinical and preclinical research.** *J Exp Clin Cancer Res* 2009, **28**(79):doi:10.1186/1756-9966-1128-1179.
31. Gaafar R, Rahman A, Aboulkasem F, El Bastawisy A: **Mistletoe preparation (Viscum Fraxini-2) as palliative treatment for malignant pleural effusion: a feasibility study with comparison to bleomycin.** *Ecanecermedicalscience* 2014, **8**:424.
32. Tröger W, Galun D, Reif M, Schumann A, Stankovic N, Milicevic M: **Viscum album [L.] extract therapy in patients with locally advanced or metastatic pancreatic cancer: a randomised clinical trial on overall survival.** *Eur J Cancer* 2013, **49**(18):3788-3797.
33. Tröger W, Galun D, Reif M, Schumann A, Stankovic N, Milicevic M: **Quality of life of patients with advanced pancreatic cancer during treatment with mistletoe-a randomized controlled trial.** *Dtsch Arztebl Int* 2014, **111**(29-30):493-502.
34. Bar-Sela G, Wollner M, Hammer L, Agbarya A, Dudnik E, Haim N: **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* 2013, **49**(5):1058-1064.
35. Grah C: **Misteltherapie bei nichtkleinzelligem Bronchialkarzinom. Randomisierte, offene Phase-II-Studie zur Untersuchung der Verträglichkeit und Wirksamkeit von Viscum-album-Extrakt in der palliativen, additiven Behandlung des fortgeschrittenen nichtkleinzelligen Bronchialkarzinoms.** GKH Havelhöhe, Akademisches Lehrkrankenhaus der medizinischen Fakultät der Charité, Universitätsmedizin Berlin; 2010.
36. Grah C, Matthes B, Happel H, Lemmens HP: **Randomisierte, offene Phase-II-Studie zur Untersuchung von Viscum album-Extrakt in der palliativen, additiven Behandlung des fortgeschrittenen nichtkleinzelligen Bronchialkarzinoms (NSCLC).** In: *Die Mistel in der Tumorthherapie 3 Aktueller Stand der Forschung und klinische Anwendung.* edn. Edited by Scheer R, Alban S, Becker H, Blaschek W, Kreis W, Matthes H, Schilcher H, Stange R. Essen: KVC Verlag; 2013: 389-401.
37. Longhi A, Reif M, Mariani E, Ferrari S: **A Randomized Study on Postrelapse Disease-Free Survival with Adjuvant Mistletoe versus Oral Etoposide in Osteosarcoma Patients.** *Evid Based Complement Alternat Med* 2014, **2014**:210198.
38. Kim KC, Yook JH, Eisenbraun J, Kim BS, Huber R: **Quality of life, immunomodulation and safety of adjuvant mistletoe treatment in patients with gastric carcinoma - a randomized, controlled pilot study.** *BMC Complement Altern Med* 2012, **12**(1):172.
39. Grossarth-Maticek R, Ziegler R: **Kontrollierte Studien zur präventiven Misteltherapie bei Myomen, Endometriosen und Cervix Dysplasie.** In: *Die Mistel in der Tumorthherapie 2 - Aktueller Stand der Forschung und klinische Anwendung.* edn. Edited by Scheer R, Alban S, Becker H, Holzgrabe U, Kemper FH, Kreis W, Matthes H, Schilcher F. Essen: KVC Verlag; 2009: 537-550.
40. Hekal IA, Samer T, Ibrahim EI: **Viscum Fraxini 2, as an adjuvant therapy after resection of superficial bladder cancer: Prospective clinical randomized study. Abstract P8.** In.; 2009: 120.
41. Tröger W, Jezdic S, Zdrle Z, Tisma N, Hamre HJ, Matijasevic M: **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* 2009, **3**:35-45.
42. Tröger W, Matijasevic M, Zdrle Z, Tisma N, Jezdic S: **Additional therapy with mistletoe extracts in breast cancer patients receiving chemotherapy: a prospective randomized open label pilot study.** In: *Die Mistel in der Tumorthherapie 2 - Aktueller Stand der Forschung und klinische Anwendung.* edn. Edited by Scheer R, Alban S, Becker H, Holzgrabe U, Kemper FH, Kreis W, Matthes H, Schilcher H. Essen: KVC-Verlag; 2009: 509-521.
43. Tröger W, Zdrle Z, Stankovic N, Matijassjevic M: **Five-Year Follow-Up of patients with early stage Breast cancer After a Randomized study comparing Additional Treatment with Viscum Album (L.) extract to chemotherapy Alone.** *Breast Cancer: Basic and Clinical Research* 2012, **6**:173.

44. Tröger W, Zdravle Z, Tisma N, Matijasevic M: **Additional therapy with a mistletoe product during adjuvant chemotherapy of breast cancer patients improves quality of life.** *Evidence Based Complementary and Alternative Medicine* 2014, In press.
45. Büssing A, Brückner U, Enser-Weis U, Schnelle M, Schumann A, Schietzel M, Hatzmann W, Hackmann J: **Modulation of chemotherapy-associated immunosuppression by intravenous application of Viscum album L. extract (Iscador): a randomised phase II study.** *Eur J Integr Med* 2008, **1**:S44-S45.
46. 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* 2008, **13** 107-120.
47. Grossarth-Maticek R, Ziegler R: **Prospective controlled cohort studies on long-term therapy of ovarian cancer patients with mistletoe (Viscum album L.) extracts Iscador.** *Arzneimittel-Forschung/Drug Research* 2007, **57** (10):665-678.
48. Grossarth-Maticek R, Ziegler R: **Wirksamkeit und Unbedenklichkeit einer Langzeitbehandlung von Melanompatienten mit einem Mistelpräparat (Iscador®)** *Schweizerische Zeitschrift für Ganzheitsmedizin* 2007, **19** 325-332.
49. Grossarth-Maticek R, Ziegler R: **Prospective controlled cohort studies on long-term therapy of cervical cancer patients with a mistletoe preparation (Iscador®)** *Forsch Komplementarmed Klass Naturheilkd* 2007, **14** 140-147.
50. Schink M, Tröger W, Dabidian A, Goyert A, Scheuerecker H, Meyer J, Fischer IU, Glaser F: **Mistletoe extract reduces the surgical suppression of natural killer cell activity in cancer patients. A randomized phase III trial.** *Forsch Komplementarmed Klass Naturheilkd* 2007, **14** (1):9-17.
51. Grossarth-Maticek R, Ziegler R: **Prospective controlled cohort studies on long-term therapy of breast cancer patients with a mistletoe preparation (Iscador).** *Forsch Komplementarmed Klass Naturheilkd* 2006, **13** 285-292.
52. Grossarth-Maticek R, Ziegler R: **Prospective controlled cohort studies on long-term therapy of breast cancer patients with a mistletoe preparation (Iscador) - Supplementary materials.** In.; 2006.
53. Auerbach L, Dostal V, Vlcek-Fleck I, Kubista E, Rosenberger A, Rieger S, Tröger W, Schierholz JM: **Signifikant höherer Anteil aktivierter NK-Zellen durch additive Misteltherapie bei chemotherapierten Mamma-Ca-Patientinnen in einer prospektiven randomisierten doppelblinden Studie.** In: *Fortschritte in der Misteltherapie Aktueller Stand der Forschung und klinischen Anwendung.* edn. Edited by Scheer R, Bauer R, Becker H, Fintelmann V, Kemper FH, Schilcher H. Essen: KVC Verlag; 2005: 543-554.
54. Enesel MB, Acalovschi I, Grosu V, Sbarcea A, Rusu C, Dobre A, Weiss T, Zarkovic K: **Perioperative application of the Viscum album extract Isorel in digestive tract cancer patients.** *Anticancer Res* 2005, **25** 4583-4590.
55. Eggermont A, Kleeberg UR, Ruiter DJ, Suci S: **European Organization for Research and Treatment of Cancer Melanoma Group trial experience with more than 2,000 patients, evaluating adjuvant treatment with low or intermediate doses of interferon alpha-2b.** In: *American Society of Clinical Oncology Educational Book.* edn. Edited by American Society of Clinical O. Baltimore, MD: Lippincott Williams & Wilkins; 2001: 88-93.
56. Kleeberg UR, Suci S, Brückner EB, Ruiter DJ, Chartier C, Linaud D, Marsden J, Schadendorf D, Eggermont AMM: **Final results of the EORTC 18871/DKG 80-1 randomised phase III trial: rIFN- α 2b versus rIFN- γ 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* 2004, **40**:390-402.
57. Piao BK, Wang YX, Xie GR, Mansmann U, Matthes H, Beuth J, Lin HS: **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* 2004, **24**(1):303-309.
58. Cazacu M, Oniu T, Lungoci C, Mihailov A, Cipak A, Klinger R, Weiss T, Zarkovic N: **The influence of Isorel on the advanced colorectal cancer.** *Cancer Biotherapy & Radiopharmaceuticals* 2003, **18** (1):27-34.
59. Borrelli E: **Evaluation of the quality of life in breast cancer patients undergoing lectin standardized mistletoe therapy.** *Minerva Medica* 2001, **92** (Suppl. 1):105-107.
60. Grossarth-Maticek R, Kiene H, Baumgartner S, Ziegler R: **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.** *Alternative Therapies in Health and Medicine* 2001, **7**(3):57-78.
61. Kim MH, Park YK, Lee SH, Kim SC, Lee SY, Kim CH, Kim YK, Kim KH, Moon HS, Song JS *et al*: **Comparative study on the effects of a Viscum album (L.) extract (mistletoe) and doxycycline for pleurodesis in patients with malignant pleural effusion.** **51th Meeting of The Korean Association of Internal Medicine.** Translation by Helixor Heilmittel GmbH. *Korean Journal of Medicine* 1999, **57**(Suppl. II):S121.
62. Dold U, Edler L, Müller HC, Müller-Wening D, Sakellariou B, Trendelenburg F, Wagner G: **Krebszusatztherapie beim fortgeschrittenen nicht-kleinzelligen Bronchialkarzinom.** Stuttgart, New York: Georg Thieme Verlag; 1991.
63. Salzer G, Danmayr E, Wutzlhofer F, Frey S: **Adjuvante Iscador-Behandlung operierter nicht kleinzelliger Bronchuskarzinome.** *Dtsch Z Onkol* 1991, **23**(4):93-98.

64. Gutsch J, Berger H, Scholz G, Denck H: **Prospektive Studie beim radikal operierten Mammakarzinom mit Polychemotherapie, Helixor und unbehandelter Kontrolle.** *Dtsch Z Onkol* 1988(4):94-100.
65. Salzer G: **30 Jahre Erfahrung mit der Misteltherapie an Öffentlichen Krankenanstalten.** In: *Misteltherapie Eine Antwort auf die Herausforderung Krebs.* edn. Edited by Leroi R. Stuttgart: Verlag Freies Geistesleben; 1987: 173-215.
66. Douwes FR, Wolfrum DI, Migeod F: **Ergebnisse einer prospektiv randomisierten Studie: Chemotherapie versus Chemotherapie plus "Biological Response Modifier" bei metastasierendem kolorektalen Karzinom.** *Krebsgeschehen* 1986, 18(6):155-163.
67. Lange O, Scholz G, Gutsch J: **Modulation der subjektiven und objektiven Toxizität einer aggressiven Chemotherapie mit Helixor. Unpublished Report.** In.; 1985.
68. Salzer G, Havelec L: **Adjuvante Iscador-Behandlung nach operiertem Magenkarzinom. Ergebnisse einer randomisierten Studie.** *Krebsgeschehen* 1983, 15(4):106-110.
69. Salzer G: **Prospektiv randomisierte Studie: Operiertes Magenkarzinom - Adjuvante Behandlung mit Iscador.** *Dtsch Z Onkol* 1988, 20(4):90-93.
70. Salzer G, Denck H: **Randomisierte Studie über medikamentöse Rezidivprophylaxe mit 5-Fluorouracil und Iscador beim resezierten Magenkarzinom - Ergebnisse einer Zwischenauswertung.** *Krebsgeschehen* 1979, 11(5):130-131.
71. Steuer-Vogt MK, Bonkowsky V, Ambrosch P, Scholz M, Neia A, Strutz J, Hennig M, Lenartz T, Arnold W: **The effect of an adjuvant mistletoe treatment programme in resected head and neck cancer patients: a randomised controlled clinical trial.** *Eur J Cancer* 2001, 37:23-31.
72. Heiny BM: **Additive Therapie mit standardisiertem Mistelextrakt reduziert die Leukopenie und verbessert die Lebensqualität von Patientinnen mit fortgeschrittenem Mammakarzinom unter palliativer Chemotherapie (VEC-Schema).** *Krebsmedizin* 1991, 12(Sonderdruck):1-14.
73. Heiny BM, Albrecht V: **Komplementäre Therapie mit Mistellektin-1-normiertem Extrakt. Lebensqualitätsstabilisierung beim fortgeschrittenen kolorektalen Karzinom - Fakt oder Fiktion?** *Die Medizinische Welt* 1997, 48:419-423.
74. Lenartz D, Dott U, Menzel J, Schierholz JM, Beuth J: **Survival of glioma patients after complementary treatment with galactoside-specific lectin from mistletoe.** *Anticancer Res* 2000, 20(3B):2073-2076.
75. Lenartz D, Stoffel B, Menzel J, Beuth J: **Immunoprotective activity of the galactoside-specific lectin from Mistletoe after tumor destructive therapy in glioma patients.** *Anticancer Res* 1996, 16:3799-3802.
76. Brinkmann OA, Lämmen G, Luboldt HJ, Hertle L, Rübbsen H: **Interferon α , interleukin 2 and 5- fluorouracil compared with mistletoe lectin in metastatic renal cell carcinoma (MRCC).** *European Urology* 2000, 37(Suppl. 2):152.
77. Lämmen G, Brinkmann OA, Luboldt HJ, Hertle L, Rübbsen H: **Interferon- α , interleukin-2 and 5- fluorouracil versus mistletoe lectin in metastatic renal cell carcinoma: Long-term results.** *European Urology* 2001, 39(Spplment 5):121.
78. Goebell PJ, Otto T, Suhr J, Rübbsen H: **Evaluation of an unconventional treatment modality with mistletoe lectin to prevent recurrence of superficial bladder cancer: a randomized phase II trial.** *The Journal of Urology* 2002, 168:72-75.
79. Semiglasov VF, Stepula VV, Dudov A, Lehmacher W, Mengs U: **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* 2004, 24:1293-1302.
80. Semiglasov VF, Stepula VV, Dudov A, Schnitker J, Mengs U: **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* 2006, 26 1519-1530.
81. Kienle GS, Kiene H: **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* 2010, 9(2):142-157.
82. Horneber MA, Bueschel G, Huber R, Linde K, Rostock M: **Mistletoe therapy in oncology.** *Cochrane DatabaseSyst Rev* 2008(2):CD003297.
83. Kienle GS, Berrino F, Büssing A, Portalupi E, Rosenzweig S, Kiene H: **Mistletoe in cancer – a systematic review on controlled clinical trials.** *Eur J Med Res* 2003, 8:109-119.
84. Kienle GS, Kiene H: **Complementary cancer therapy: a systematic review of prospective clinical trials on anthroposophic mistletoe extracts.** *EurJ Med Res* 2007, 12(3):103-119.
85. Kienle GS, Glockmann A, Grugel R, Hamre HJ, Kiene H: **[Clinical research on anthroposophic medicine:update of a health technology assessment report and status quo].** *Forsch Komplementarmed Klass Naturheilkd* 2011, 18(5):269-282.
86. Mabeed M, El-Helw L, Sharma S: **Phase II study of viscum fraxini-2 in patients with advanced hepatocellular carcinoma.** *Br J Cancer* 2004, 90:65-69.
87. Mahfouz MM, Ghaleb HA, Zawawy A, Scheffler A: **Significant tumor reduction, improvement of pain and quality of life and normalization of sleeping patterns of cancer patients treated with a high dose of mistletoe.** *Ann Oncol* 1998, 9(S2):129.

88. Mahfouz MM, Ghaleb HA, Hamza MR, Fares L, Moussa L, Moustafua A, El-Za Wawy A, Kourashy L, Mobarak L, Saed S *et al*: **Multicenter open labeled clinical study in advanced breast cancer patients. A preliminary report.** *Journal of the Egyptian NatCancer Inst* 1999, **11** (3):221-227.
89. Seifert G, Tautz C, Seeger K, Henze G, Laengler A: **Therapeutic use of mistletoe for CD30+ cutaneous lymphoproliferative disorder / lymphomatoid papulosis.** *J Eur Acad Dermatol Venereol* 2006, **21** 1-2.
90. Werthmann PG, Helling D, Heusser P, Kienle GS: **Tumour response following high-dose intratumoural application of Viscum album on a patient with adenoid cystic carcinoma.** *BMJ Case Reports* 2014:doi: 10.1136/bcr-2013-203180.
91. Werthmann PG, Sträter G, Friesland H, Kienle GS: **Durable Response of Cutaneous Squamous Cell Carcinoma Following High-dose Peri-lesional Injections of Viscum album Extracts - A Case Report.** *Phytomedicine* 2013, **20**:324-327.
92. Orange M, Fonseca M, Lace A, von Laue HB, Geider S: **Durable tumour responses following primary high-dose induction with mistletoe extracts: Two case reports.** *Eur J Integr Med* 2010, **2**:63-69.
93. Orange M, Lace A, Fonseca M, von Laue HB, Geider S, Kienle GS: **Durable Regression of Primary Cutaneous B-cell Lymphoma following Fever-inducing Mistletoe Treatment - Two Case Reports.** *Glob Adv Health Med* 2012, **1**(1):16-23.
94. von Schoen-Angerer T, Wilkens J, Kienle GS, Kiene H, Vagedes J: **High-Dose Viscum album Extract Treatment in the Prevention of Recurrent Bladder Cancer: A Retrospective Case Series.** *Perm J* 2015, **19**(4):76-83.
95. Kirsch A: **Successful treatment of metastatic malignant melanoma with Viscum album extract (Iscador M).** *J Altern Complement Med* 2007, **13**(4):443-445.
96. Rose A, El-Leithy T, vom Dorp F, Zakaria A, Eisenhardt A, Tschirdewahn S, Rubben H: **Mistletoe Plant Extract in Patients with Nonmuscle Invasive Bladder Cancer: Results of a Phase Ib/Ila Single Group Dose Escalation Study.** *J Urol* 2015, **194**(4):939-943.
97. Kienle GS, Mussler M, Fuchs D, Kiene H: **Intravenous Mistletoe Treatment in Integrative Cancer Care: A Qualitative Study Exploring the Procedures, Concepts, and Observations of Expert Doctors.** *Evid Based Complement Alternat Med* 2016, **2016**:4628287.
98. Kienle GS, Mussler M, Fuchs D, Kiene H: **Individualized Integrative Cancer Care in Anthroposophic Medicine: A Qualitative Study of the Concepts and Procedures of Expert Doctors.** *Integr Cancer Ther* 2016.
99. Sugarman J: **Are mistletoe extract injections the next big thing in cancer therapy?** *Johns Hopkins Magazine* 2014, **2016**(May 1sts).
100. Rexer H, Geschäftsstelle der AUO: **[Study on the treatment of nonmuscle invasive bladder cancer: A phase III efficacy study for intravesical instillation of mistletoe extract in superficial bladder cancer (TIM) AB 40/11 of the AUO].** *Urologe A* 2015, **54**(3):406-408.
101. 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* 2011, **11**(1):72.
102. Steele ML, Axtner J, Happe A, Kroz M, Matthes H, Schad F: **Adverse Drug Reactions and Expected Effects to Therapy with Subcutaneous Mistletoe Extracts (Viscum album L.) in Cancer Patients.** *EvidBased Complement AlternatMed* 2014, **2014**:724258.
103. Steele ML, Axtner J, Happe A, Kroz M, Matthes H, Schad F: **Use and safety of intratumoral application of European mistletoe (Viscum album L) preparations in Oncology.** *Integr Cancer Ther* 2015, **14**(2):140-148.
104. Steele ML, Axtner J, Happe A, Kroz M, Matthes H, Schad F: **Safety of Intravenous Application of Mistletoe (Viscum album L.) Preparations in Oncology: An Observational Study.** *Evid Based Complement Alternat Med* 2014, **2014**:236310.
105. Stein GM, Pfüller U, Schietzel M, Büßsing A: **Toxic proteins from European mistletoe (Viscum album L.) : increase of intracellular IL-4 but decrease of IFN- g in apoptic cells.** *Anticancer Res* 2000, **20**(3A):1673-1678.
106. Stein GM, Berg PA: **Adverse effects during therapy with mistletoe extracts.** In: *Mistletoe The Genus Viscum* edn. Edited by Büßsing A. Amsterdam: Hardwood Academic Publishers; 2000: 195-208.
107. Shakeel M, Trinidad A, Geider S, Ah---See KW: **The case for mistletoe in the treatment of laryngeal cancer.** *The Journal of Laryngology & Otology* 2014, **128**:302---306