Mistletoe & Cancer

MOA: Cytokines

- A shift from Th1 to Th2 cell function is characteristic of the unfavorable immune changes of cancer [1]
- A number of in vitro, animal and human studies have demonstrated enhanced production of both Th1 and Th2 cytokines [2, 3, 4]

MOA: Cytokines

- Mice implanted with melanoma tumors were treated with Mistletoe extract
- Tumor inhibition was associated with production of the Th1 cytokine IL-12
- Anti-tumor effects were abolished in IL-12 deficient mice. [5]

MOA: Cytokines

- A group of cancer patients (7 stage I-II and 9 stage III-IV) were treated with Mistletoe for 4 weeks

- Assessment of Th1 and Th2 cytokines at baseline and throughout treatment was made and compared to healthy controls

MOA: Cytokines

- IL-12 levels were 3 fold higher than controls at baseline. Levels increased (borderline significance) after Mistletoe treatment

- INF-gamma (produced by Th1 & NK cells) was 3 fold lower than controls at baseline. After treatment, levels increased 2 fold

MOA: Cytokines

- IL-2 levels were 9 times lower in cancer patients compared with controls at baseline
- IL-2 levels significantly increased (2.8 fold) with Mistletoe treatment
- IL-4 levels were low in both patients and controls. There was no change with tx [6]

MOA: Cytokines

- Lymphoma patients treated with Mistletoe were assessed for levels of IL-6, sIL-6r, and sgp130 and compared with controls.

- IL-6 levels were significantly reduced and sgp130 significantly raised in the long term Mistletoe therapy group. [7]

MOA: Immune Cell Modulation

- Several animal and human studies have demonstrated significant increases in Natural Killer cell numbers and activity as well as other immune cells, after treatment with mistletoe extracts. [8, 9]

MOA: Immune Cell Modulation

- Twelve patients with various cancers were treated with AME (standardized lectins) twice weekly for 48 weeks.

- All immune indices (monocytes, lymphocytes, CD4, CD8, NK cells and activity) were raised throughout 6-48 months of treatment.

MOA: Immune Cell Modulation

- NK cell count rose significantly 35% compared to baseline.
- NK cell counts remained elevated by 11% 6 weeks after discontinuing treatment.
- NK cell factor (total ex vivo activity) increased up to 50% with treatment. [9]

MOA: Cytotoxic Effects

- In vitro, at very low concentrations (0.17-1 ng) Mistletoe extract is highly cytotoxic to many solid and hematological malignancies.

- Compared with doxorubicin, Mistletoe extract is 3 to 4 logs more potent against human breast tumors [10]

MOA: Cytotoxic Effects

- Human pancreatic cancer xenografts were injected intratumorally with lectin rich mistletoe extract or treated with I.V. Gemcitabine.
- Bi-weekly injections of Mistletoe resulted in 3/8 complete remissions and 3/8 partial remissions. Gemcitabine was less active: 1/8 complete & 2/8 partial remissions. [11]

Enhancing Chemotherapy

- Mistletoe extracts enhance cytotoxic effects of vincristine, mafosfamide, idarubicin and cisplatin in human leukemia cell lines. [12]
- Synergistically enhance paclitaxel in liver cancer cells. [13]
- Enhances doxorubicin, cisplatin and taxol in lung cancer cells [14] cyclophosphamide in breast cancer [15] and etoposide leukemia [16]

Enhancing Radiotherapy

- Mistletoe prevented damage to healthy tissue and significantly accelerated the healing process in animals [17] and patients treated with radiotherapy. [18]

- Mistletoe extract enhanced the effectiveness of ionizing radiation in vitro. [19]

Enhancing Radiotherapy

- Fibrosarcoma tumor xenografts were treated with radiation alone or in combination with Mistletoe extract.

- A complete tumor responses occurred in 25% of animals treated with radiation. In combination with Mistletoe extract complete responses increased to 65% [20]

Systemic Review: 138 Clinical trials 23 Prospective Controlled Trials [21]

12 Studies:	7 Studies:	3 Studies:	1 Study:
Statistically significant positive results in Mistletoe group	Positive trend in Mistletoe Group	No difference to Mistletoe Group	Negative Trend

Kienle et al., Eur J Med Res 2003, 8: 109-119

Melanoma & Mistletoe

EORTC 18871/DKG 80-1 randomized phase III trial:rIFN- a2b versus rIFN-g versus ISCADOR M1 versus observation after surgery in melanoma patients with either high-risk primary (thickness >3 mm) or regional lymph node metastasis.

Eur J Cancer. 2004 Feb;40(3):390-402.

Melanoma & Mistletoe

- 102 subjects were treated w mistletoe for 1 year and followed for 8 years. (n=~240 in each INF arm)
- Results: None of the treatment groups showed improvements in survival or other outcome measures. [22]

Melanoma & Mistletoe

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

Arzneimittelforschung. 2005;55(1):38-49

Melanoma & Mistletoe

- Multicenter, comparative, retrolective, epidemiological, cohort study with parallel group design.
- In accordance with Good Epidemiological Practice guidelines and the IFAG (SOPs) for retrolective cohort studies.
- Can meet the Evidence Based Medicine requirements with evidence level II

Melanoma & Mistletoe

- 686 subjects were treated with surgery alone or surgery plus FME
- The mistletoe group was treated for 2.5 years.
- Subjects were followed for up to 10 years.

Melanoma & Mistletoe

Survival Analysis (Mistletoe vs Control)

- Tumor related Survival: 59% ↓ in risk of tumor related death.
- Overall Survival: 36% ↓ in the risk of death.
- Disease-Free Survival: Risk of disease recurrence after treatment ↓ 27%.
- Brain Metastasis-Free Survival: 67% ↓ in the risk of brain metastasis [23]

Melanoma & Mistletoe

RCT vs Cohort

- 50% Stage III in RCT, only 8% in Cohort.
- Pt's in RCT tx with Iscador M. >80% tx with Iscador P. Pini indicated for melanoma
- Tx </= 1 year in RCT. Cohort 2.5 years.
- RCT insufficient test power at 5 years & beyond. Cohort >80% validity at > 5years.
- Unusual dose schedule: Series 0 x 14 days then 20mg for 28 days. Is that possible?
- RCT funded in part by Drug manufacturers.

Mistletoe & Breast Cancer

Efficacy and Safety of Long-term Complementary Treatment with Standardised European Mistletoe Extract (Viscum album L.) in Addition to the Conventional Adjuvant Oncological Therapy in Patients with Primary Non-metastatic Breast Cancer

Arzneimittelforschung. 2004;54(8):456-66.

Mistletoe & Breast Cancer

- The multi-center, comparative, retrolective, epidemiological cohort study with parallel groups design and randomly selected centers was carried out according to Good Epidemiological Practice (GEP) rules.

Mistletoe & Breast Cancer

- 1442 patients with non-metastatic breast cancer.
- 710 were treated after surgery with mistletoe extract in addition to conventional chemo-, radio- or hormonal therapy.
- 732 matched controls were treated with conventional therapy alone.

Mistletoe & Breast Cancer

- Median observation period was 5.5 years (Mistletoe) and 5 years (control).
- Median Mistletoe treatment duration was 4.3 years.

Mistletoe & Breast Cancer

Results

- Adverse drug reactions - from conventional treatments - were significantly reduced by 53% in the mistletoe group.

- Patients free of symptoms at the end of the post operative phase were significantly greater in the mistletoe group (78% vs 38%)

Mistletoe & Breast Cancer

Results

- The overall estimated survival was significantly longer for the mistletoe group (adjusted mortality hazard ratio (95 % CI): HR = 0.46 (0.22−0.96), p = 0.038). (i.e. Risk of death reduced by 54%) [24]

Mistletoe & Glioma

Survival of Glioma Patients after Complementary Treatment with Galactoside-Spedific Lectin from Mistletoe

Anticancer Res. 2000 May-Jun;20(3B):2073-6

Mistletoe & Glioma

- Prospective randomized trial of 38 patients with primary brain tumors.
- All patients were treated with surgery, radiation and dexamethasone.
- Patients received mistletoe therapy (n=20) or conventional treatment alone (n=18) and were followed for >4 years.

Mistletoe & Glioma

Results

- 1 day post-surgery Lymphocyte subsets (CD3+, CD4+, CD8+), NK cells and activities (CD25+, HLA/DR+) declined on average by 47.5%
- At 3 months control group values returned to pre-surgery levels. The Mistletoe group had a 66.2% average increase over pre-surgery levels.

Mistletoe & Glioma

Results

- Spitzer Quality of life measures: At 6 months the control group declined by 31% from pre-surgery levels.

- The mistletoe group had a significantly improved, returning to pre-surgery levels by 6 months.

Mistletoe & Glioma

Results

- Among stage III & IV patients, relapse free survival was greater for the mistletoe group (17.43 vs 10.45 months).

- The overall survival was significantly greater for the mistletoe group (20.05 vs 9.90 months). [25]

Mistletoe & Colon Cancer

Treatment of Advanced Colorectal Carcinoma - Examination of the Efficacy of the Combination of 5-FU and Folinic Acid vs 5-FU and Folinic Acid in Combination with an Optimized Helixor Treatment

Dtsch. Zschr. Onkol. 1988;20(3):63-7

Mistletoe & Colon Cancer

- Patients with either metastasis or recurrence of colorectal cancer were treated with either chemotherapy in combination with Mistletoe (n=19) or chemotherapy alone (n=20).

- Patients were enrolled from 1983 to 1985 and followed until 1987.

Mistletoe & Colon Cancer

- Groups were equally matched according to Dukes stage and tumor location.
- Response rates were defined as Complete remission, partial remission, or minimal change.
- Stable disease and progressive disease were classified as non-response.

Mistletoe & Colon Cancer

Results	CR	PR	MC	SD	PD
Controls	0	6	4	3	7
Helixor	3	7	5	3	1

Response rate (CR + PR + MC)
Control = 50%
Helixor = 78.95%

Mistletoe & Colon Cancer

Results

- Median survival time for Mistletoe and control groups were 26 vs 14 months.

- In 9/87 all control patients had died, while 5 patients treated with Mistletoe were still alive. [26]

Mistletoe Case

- 55 y.o. Dx metastatic breast cancer to LN's, sacrum, femor, T2, 5, 11 and pelvic region. 6/03
- Tx: 3 rounds AC - No response. CA27.29 is 98.
- Follows with 2 rounds of Taxotere and Xeloda - CT scan shows stable disease and slight shrinkage. CA27.29 = 93
- Does 1 more round of Taxotere and stops Xeloda after 1 dose: hand & foot syndrome, severe mouth ulcers and diarrhea. Refuses further chemo. 11/28/03. CA27.29 = 81.

Mistletoe Case

- 12/4/03 Begins IVC 50g. Hands feeling much better after IVC. After 3 treatments, start IVC/K3 twice weekly for 3 weeks. Begins 12 treatments of radiotherapy to sacrum.
- 1/5/04 Iscador Mali - Trained pt. To self inject.
- 2/16/04 Oncologist reports significant shrinkage all tumors. Right breast mass: 2.1 x 1.7 was 3.3 x 2.2 cm. CA27.29 = 58. No chemo for 2.5 months.
- 2/19/04 - Begins Faslodex injections.
- 3/4/04 - CA27.29 = 45

Mistletoe Case

- 4/26/04 - CA27.29 = 37 (RR 0-40).
- 10/4/04 Oncologist says she can't palpate tumor. CA27.29 = 20. Pt. D/C's Faslodex.
- 8/8/06 - Continues with Iscador and supplements.. CA27.29 consistently under 20 since 10/04. No IVC/K3 since 10/05.

Mistletoe & Cancer

Fin

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Enhancing chemo therapy

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