HELIXOR
Spezialist für Misteltherapie

Summary of the current level of scientific knowledge on cancer treatment with the HELIXOR™ mistletoe preparations

HELIXOR™ preparations are pure, sterile-filtered, aqueous fresh plant extracts from *Viscum album L.* The standardized manufacturing process according to GMP-guidelines as well as regular physical, chemical and biological quality controls (including the MOLT-4-bioassay testing the cytotoxic activity of the whole extract on MOLT-4-leukaemia cells) insure a consistently high and uniform batch quality.

After several years of clinical testing, the HELIXOR™ preparations were first registered in Germany in 1976 and then again in 1982 according to the new German drug law (AMG) requiring the proof of efficacy and safety. To date, the HELIXOR™ preparations are registered in Austria, Switzerland, Luxembourg, Sweden, Finland, Latvia, Lithuania, Korea, China, Russia, Chile and Peru.

Pharmacological effects of HELIXOR™ and other mistletoe preparations are carefully examined and published in some hundred scientific papers:
- Dose dependent cytotoxicity in cell cultures by induction of apoptosis.
- Inhibition of tumour growth and metastases in animals.
- Immunomodulation: activation of macrophages, dendritic cells and natural killer cells, increase in phagocytosis and burst activity, increase in numbers of eosinophils, lymphocytes and T-helper cells.
- DNA stabilisation in peripheral blood mononuclear cells resulting in a significant protection from immunosuppressive effects of chemotherapy.
- Inhibition of tumour angiogenesis.

A summary of the results of experimental research is given by Büssing (1).

Evidence for efficacy of HELIXOR™ as an adjunctive treatment in cancer patients is shown by the monograph *Viscum album* provided by the C-Commission, Federal Health Administration, Germany (2), 24 clinical studies (3-26) and numerous case reports.

Clinical trials primarily examined the efficacy of high-dose palliative HELIXOR™ treatment in inoperable or metastasizing tumours:

- In a **retrospective study in inoperable rectal and colon cancer** *median survival was significantly prolonged* with HELIXOR™ monotherapy from 4.8 to 8.6 months (colon cancer) and from 4.8 to 11 months (rectal cancer) in comparison with untreated control. One-year survival increased from 12.8% to 44.4 % ($p < 0.001$). Furthermore, an improved quality of life was achieved in 74 % of patients treated with HELIXOR™ (3).

- A **retrospective study in liver metastases** of various primary tumours (colon, rectal, gastric and pancreatic cancer) yielded similar results as in the study mentioned above: median survival 8.1 versus 2.5 months, one-year survival 40.3 versus 6.6 % ($p < 0.001$) (4).

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The efficacy of HELIXOR™ in combination with chemotherapy was examined in 4 clinical studies *for palliative treatment:*

- In a **prospective randomized trial, patients with metastasizing colorectal cancer** were treated with 5-FU and folinic acid. Adjunctive HELIXOR™ treatment resulted in a *distinct prolongation of survival to almost double* in comparison to chemotherapy alone. However this big difference in survival was not significant due to the small patient numbers in this pilot study (5).

- **A further prospective controlled study** fully confirmed this positive result. Further, a *significantly higher response rate* was demonstrated in the HELIXOR™ group in comparison to the control group. This result argues in favour of an increased efficacy of chemotherapy by combination with HELIXOR™ (6).

- A *distinct prolongation of median survival* by additive HELIXOR™ treatment was also achieved in **30 patients with chronic myeloid leukaemia**: median survival in patients treated with both chemotherapy (Busulfan) and HELIXOR™ was 55.7 months in comparison to 30 months in a historic control group which had a comparable prognostic structure and was only treated with Busulfan (7).

- The efficacy of an adjunctive mistletoe treatment in **malignant lymphoma and chronic leukaemia** was analysed in a **retrospective study with 700 patients**: additional treatment with mistletoe extract resulted in a *clear, but not statistically significant, prolongation of median survival* (11.4 years, versus 8.6 years in patients without mistletoe therapy). In addition, patients reported an improved quality of life. Frequently voiced theoretical objections concerning a possibly unfavourable impact of mistletoe therapy on the course of malignancies of the lymphatic and haematopoetic system are refuted by this study (8).

Not only efficacy but also tolerance of chemotherapy can be improved with an adjunctive mistletoe therapy:

- In a **prospective randomized pilot study, 44 patients with inoperable ovarian cancer, squamous cell lung carcinoma or head and neck cancer** were treated with aggressive chemotherapy (ifosfamide, cisplatin) combined with radiation.
  Adjunctive treatment with HELIXOR™ resulted in a significantly improved quality of life measured by Karnofsky performance index ($p < 0.001$) as well as in less nausea ($p = 0.005$), vomiting ($p = 0.08$) and cancer pain ($p = 0.04$). Recovery of leukopoesis was significantly quicker in the HELIXOR™ group ($p = 0.003$). Hence, the full planned dose of chemotherapy was more frequently applied in the HELIXOR™ group than in the control group. This may account for the higher remission rate of 78.2 % in the HELIXOR™ group compared to 61.9 % in the control group (9).

- The preliminary results of this pilot study could be confirmed in a **prospective randomized multicentre study in 233 patients with breast, ovarian or non-small cell lung cancer** according to valid standard methods and following the guidelines of good clinical practise (GCP): All patients were treated with standard polychemotherapy. Patients who were additionally treated with HELIXOR™ A had a *significantly better quality of life and a better tolerance of chemotherapy* in comparison to the control group consistently confirmed by means of three different

quality of life indices (p = 0.01/0.0007/0.003, FLIC-/TCM-/KPI-Index) and the analysis of adverse events (10).

- **In a prospective randomized double-blinded pilot study, 23 patients with operated breast cancer stage I or II** were treated with 6 courses of adjuvant chemotherapy (CMF). Patients additionally treated with placebo showed a significant decrease of natural killer cell activity during chemotherapy. In contrast, patients additionally treated with HELIXOR™ A had a *significant higher natural killer cell activity* (p = 0.0005) indicating that HELIXOR™ A is effective in the reduction of the immunosuppressive side effects of chemotherapy.
  It was additionally shown that a doubled-blinded design is not suitable for the evaluation of subcutaneous mistletoe therapy, because patients as well as doctors were deblinded by the evidence of the typical local inflammatory reaction at the site of subcutaneous mistletoe injection (11).

- This **prospective randomized phase III trial** comprised the results **of 89 post-surgical patients with breast cancer, starting treatment with CAF**. The patients of one group received additional mistletoe therapy (HELIXOR™ or another mistletoe preparation) or no additional treatment. *The mistletoe group had a significantly better quality of life* in 5 of 15 EORTC-QLC C30-dimensions (pain, diarrhoea, role function, insomnia, nausea/vomiting). Furthermore, a trend towards better quality of life was found in another 5 dimensions (12).

Efficacy was also proven for adjuvant HELIXOR™ treatment after complete cancer surgery:

- In **643 patients with operated breast cancer** the prognosis-improving effect of HELIXOR™ was examined in a prospective controlled multicentre study: Here treatment with HELIXOR™ or polychemotherapy (CMF/O) yielded a significant prolongation of survival (p = 0.032) in comparison to the control group without chemotherapy or HELIXOR™. The clearest impact of HELIXOR™ treatment on survival was shown in patients with axillary lymph node metastases (13).

- In a **retrospective study in 794 patients with operated breast cancer stage II-IV,** adjunctive mistletoe therapy resulted in a significantly longer survival in stage III and IV ($p < 0.05$), but not in stage II. Comparing different adjuvant treatments the combination of mistletoe and radiation was the most effective regarding recurrence rate, disease free interval and median survival (14).

- Only a marginally longer survival could be demonstrated in **516 patients with breast cancer stage I** (5-years survival 91 % in the mistletoe group in comparison to 83 % in the untreated control group) (15).

- In a further **retrospective analysis of 1246 patients with operated breast cancer** additionally treated with mistletoe preparations, the results of the former three studies could be generally confirmed: In comparison to patients of the Munich Cancer Register the 10-years survival rate was 73.3 % versus 54 %. Only in stage I an increased survival could not be demonstrated (88.1 % versus 90 %). The advantage of the mistletoe group increased with cancer staging: 10-years survival 71.6 % versus 65 % for stage II, and 55.6 % versus < 30 % for stage III (16).

- In a **retrospective study in 421 patients with operated stomach cancer** adjunctive mistletoe treatment resulted in a clear prolongation of median survival: In patients without lymph node metastases median survival was prolonged by 20 months in comparison to untreated control and by 8 months in comparison to adjuvant chemotherapy. In patients with lymph node metastases, survival was prolonged by 6 months, which was comparable to the effect of adjuvant chemotherapy (17).

- In a **retrospective analysis of 695 patients with operated colorectal cancer** median survival was prolonged by adjuvant mistletoe therapy by 41 months in stage I-II (N0) and by 17 months in stage III (N1-2 M0). In far advanced colorectal cancer (N3 or M1) the combination of mistletoe and chemotherapy was more effective than mistletoe or chemotherapy alone (18).

- A further **retrospective study** of the same centre compiled **991 patients with operated colorectal cancer**. Here, recurrence rate was significantly lower in patients treated with adjuvant mistletoe therapy: compared with untreated controls, recurrence rate was reduced by 13 % in rectal cancer without lymph node metastases and by 23 % in lymph node positive colon cancer. Additionally, median survival was prolonged, most markedly in rectal cancer without lymph node metastases (213 days) and in lymph node positive colon cancer (340 days) (19).

- In a **retrospective analysis of 284 melanoma patients** complete data for evaluation were available in 94 patients. Sixty-six of these patients were treated with mistletoe preparations. In spite of a significantly worse prognosis of the mistletoe group (proven metastases in 33.3% of the patients before HELIXOR™ treatment compared to 0% metastases in the control group) survival rates in the mistletoe group were comparable with those of control groups from the literature (5-years survival 80 %, 10-years survival 68 %) (20).

- In **retrospective studies**, the efficacy of mistletoe therapy on the survival time of patients with 5 different malignant diseases **(lymphoma/leukaemia, pancreas cancer, malignant melanoma, breast cancer and colorectal cancer)** was investigated. Survival time of patients who were treated with a mistletoe preparation (HELIXOR™ or another mistletoe preparation) up to 10 years in an outpatient clinic (Community hospital Herdecke) were compared with the survival time of patients of a cancer registry ("Epidemiologisches Krebsregister Saarland") with unknown therapy. Within the 5 tumour entities, the *patients with mistletoe therapy showed a significant longer survival time* than the patients from the tumour registry (21).

- In a **controlled pharmacoepidemiological cohort study in 741 breast cancer patients** after termination of adjuvant radio-/chemotherapy, HELIXOR® treatment resulted in a significantly lower frequency of therapy- or disease-related complaints as compared to the control group frequency ($p<0{,}001$). A clear increase of this HELIXOR®-related benefit was seen from year to year during the 5-year treatment period. Especially the the frequency of complaints from pain, fatigue and mucositis decreased. (22).

In two further studies, the *efficacy of high-dose intrapleural HELIXOR™ instillation in malignant pleural effusion* was evaluated:

- In a **prospective study with 20 consecutive hospitalized patients with pleural effusion in far advanced cancer**, complete remission according to WHO criteria could be achieved in 72 %, together with an excellent tolerance of HELIXOR™ instillation (side effect rate 1.2 % WHO grade 1). The decrease in pleural effusion volume and cancer cells within the effusion was significantly dependent on the frequency and dose of HELIXOR™ instillations ($p < 0.001$) (23).

- In a **prospective randomized study including 30 patients with malignant pleural effusion** high-dose HELIXOR™ instillation resulted in a significantly higher response rate in comparison to standard therapy with doxycycline (91 % versus 66.6 %, $p < 0.05$). In addition, the side effect index was significantly lower ($p < 0.05$) (24).

Currently HELIXOR™ will be administered intralesionally in a growing number.

- In a **pilot study**, the efficacy of **intratumoural injection of** HELIXOR™ **M was investigated in 6 patients with hepatocellular carcinoma and in 21 patients with liver metastases** of colorectal cancer.
  Using ultrasound control, 100 – 2,500 mg HELIXOR® M was injected into the liver tumours one to three times weekly. In hepatocellular carcinoma, tumour remission could be achieved in 83 % of patients, combined with a significant decrease of the tumour marker AFP. In the patients with liver metastases, a decline in the tumour marker and a remission of the metastases was achieved in 52 % of cases (25).

- In a further **pilot study the effect of HELIXOR™ M on inoperable pancreatic cancer was evaluated in 12 patients**. HELIXOR® M was applicated intralesionally by endoscopic ultrasound-guided fine-needle injection.
  According to the WHO response criteria, 8 % of the patients showed complete response, 50 % partial response and 33 % no change. This remission rate is superior to chemotherapy in inoperable pancreatic cancer (about 10 %). No major toxicity was observed. Quality of life improved in more than 83 % (26).

Scientific acceptance of a treatment method can be reflected by the number of scientific publications: there are to date over 187 publications on HELIXOR™, most of them describing pharmacological effects, among them 35 theses and dissertations and 1 postdoctoral thesis from German universities as well as 58 peer-reviewed papers published in international scientific journals.

In the book "Grundlagen der Komplementäronkologie [fundamentals of complementary oncology]" edited by Prof. Dr. med. Joseph Beuth, director of the Institute for Scientific Evaluation of Naturopathy at the University of Cologne, mistletoe therapy is classified as a well founded and recommendable complementary oncological treatment (27).

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In the standard work of mistletoe investigation from Kienle/Kiene "Die Mistel in der Onkologie – Fakten und konzeptionelle Grundlagen [mistletoe in oncology – facts and basic conceptions]", Schattauer Verlag Stuttgart New York 2003, the results of scientific mistletoe research are summarised on 749 pages and critically discussed. The most important results of HELIXOR™ research as well as many case reports are described and mainly affirmed in this book (28).

The potential improvement in survival due to HELIXOR™ treatment is particularly attractive due to the simultaneous improvement in quality of life (3-5, 8-10, 16, 22).

In **three critical reviews** (28,29,30) of clinical trials concerning mistletoe therapy 8 of the described HELIXOR™ studies showing an improvement of survival were classified as valid (3-7, 9,11,13) and 5 studies who showed an increasing quality of life as valid, too (3,4,10,11,31). Whereas 10 studies have not been qualified as valid. The remaining studies were not yet analysed.

Evidence for efficacy of HELIXOR™ as a complementary treatment in cancer patients is shown by the recent **Cochrane Review** on mistletoe therapy in oncology (32). According to this report, 14 out of 16 randomized trials investigating the impact of mistletoe therapy on quality of life and 6 out of 13 trials investigating survival showed some evidence of benefit. In general the studies show a good tolerability of mistletoe treatment and only few adverse effects. In this analyses 4 HELIXOR™ studies (5,10,11, 31) were included which are consistent with the high profile of the Cochrane Collaboration.

HELIXOR™ is also mentioned in **oncological standard works**: In the comprehensive German two-volume reference of oncology, edited by Hiddemann, Huber and Bartram, Springer Verlag Heidelberg New York 2004, mistletoe preparations including HELIXOR™ are named in chapter 25.2.3 and three HELIXOR™ trials are reported (33).

Scientific acceptance of a treatment is also reflected by the **frequency of application**: According to a multicentre cross-sectional study performed in different German rehabilitation hospitals, 58.4 % of cancer patients used methods of complementary medicine, mostly mistletoe preparations (61.6 %) (34). This is in accordance with yearly statistics of the prescriptions of cytostatic drugs within the National German Health Insurance System: HELIXOR™ is ranked third in the list of the most frequently prescribed cytostatic drugs (35). The costs for HELIXOR™ prescribed for cancer patients continue to be refunded by the German National Health Insurances.

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