Helixor®

Mistletoe Therapy for
Tumor Patients

Integrative Mistletoe Therapy with Helixor®

Basis of Scientific Approval

Helixor
Bringing life to life.

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Helixor® mistletoe products are pure, sterile filtered, aqueous fresh plant extracts of *Viscum album* L. (white-berry mistletoe).

Standardized manufacturing processes as well as continuous physical, chemical and biological quality control (including assessment of cytotoxic effects on MOLT-4 leukemia cells to determine the biological activity of the mistletoe product) guarantee a consistent batch-to-batch quality.

Pharmacological Effects

The pharmacological effects of Helixor® have been described in over 120 scientific publications.

Overview of the pharmacological effects of Helixor®

Effects	Clinical Relevance
Immunomodulation: activation of macrophages, dendritic cells, NK cells, increase of phagocytosis, increase in eosinophils, lymphocytes and T helper cells	Reduced susceptibility to infections, indirect immune-mediated tumor inhibition
Immunoprotection (DNA stabilization, exclusively in lymphocytes but not in tumor cells)	Better tolerability of chemotherapy, less immunosuppression by chemotherapy
Neuroendocrine effects	Improved quality of life (especially fatigue)
Tumor inhibition (apoptosis ↑, angiogenesis ↓)	Prolongation of survival time, tumor regression in specific cases

In clinical practice, this translates into:

- Improvement of general condition and quality of life through
  - Increased performance and vigor
  - Normalized body rhythms including body temperature, sleep and digestion
  - Increased appetite
  - Reduced nausea and vomiting
  - Emotional well-being
  - Reduced depression and anxiety
- Reduction of adverse reactions to conventional therapies (e.g. chemo- or radiotherapy), in particular cancer-related fatigue
- Alleviation of tumor-related pain
- Prevention of relapse and metastasis

Study Situation

Efficacy and safety of Helixor® were shown in a positive monograph published by the Commission C of the German Department of Public Health,[22] in 27 clinical studies[1 – 12, 23 – 29, 31, 32, 34 – 38, 42] as well as in numerous case reports. Three further studies have been conducted on off-label use.[14, 21, 39]

Summary of all studies involving Helixor®

		Number of studies
Methodology	• Prospective randomized	10
	• Prospective nonrandomized	6
	• Retrospective	14
Tumor type*	• Breast	9
	• Colorectal	6
	• Others	4
	• Several entities	11
Indication*	• Palliative therapy in inoperable/ metastasizing tumors	20
	• Prevention of relapse	18
Parameters	• Survival	16
	• Quality of life	14
	• Side effects of oncological therapies	8
	• Immune parameters	4
	• Response rate	5
	• Relapse rate	1
Results	• Advantage with Helixor® compared to controls	21
	• Significant advantage	15
	• Trend	6
	• No advantage	4
	• Single-arm cohort studies with significant improvement	2

Total: 30 clinical trials, 5,962 patients**

* multiple references possible
** without control groups

Update February 2016

Verified improvement of tolerability of chemotherapy

The study conducted in the USA under the auspices of the **National Center for Complementary and Alternative Medicine (NCCAM)** and in collaboration with the National Cancer Institute (NCI) particularly investigated the possible interactions between cytostatic agents and herbal medicinal products, specifically in the combination of Helixor® A with gemcitabine, used primarily as palliative chemotherapy for far advanced solid tumors.

Study aim	Influence of Helixor® A on the pharmacokinetics, pharmacodynamics and safety of gemcitabine hydrochloride (Gemzar®)
Indications	Far advanced solid tumors (stage IV) (pancreas, colorectal, NSCLC, breast)
Study design	Two-part, monocentric phase I dose escalation study
Patients	44 patients (21 f, 23 m, age 29 – 81) Chemotherapy and/or radiotherapy (n = 33), without preceding treatment (n = 11)
Authors	Mansky PJ, Wallerstedt DB, Sannes TS, Stagl J, Johnson LL, Blackman MR, et al.

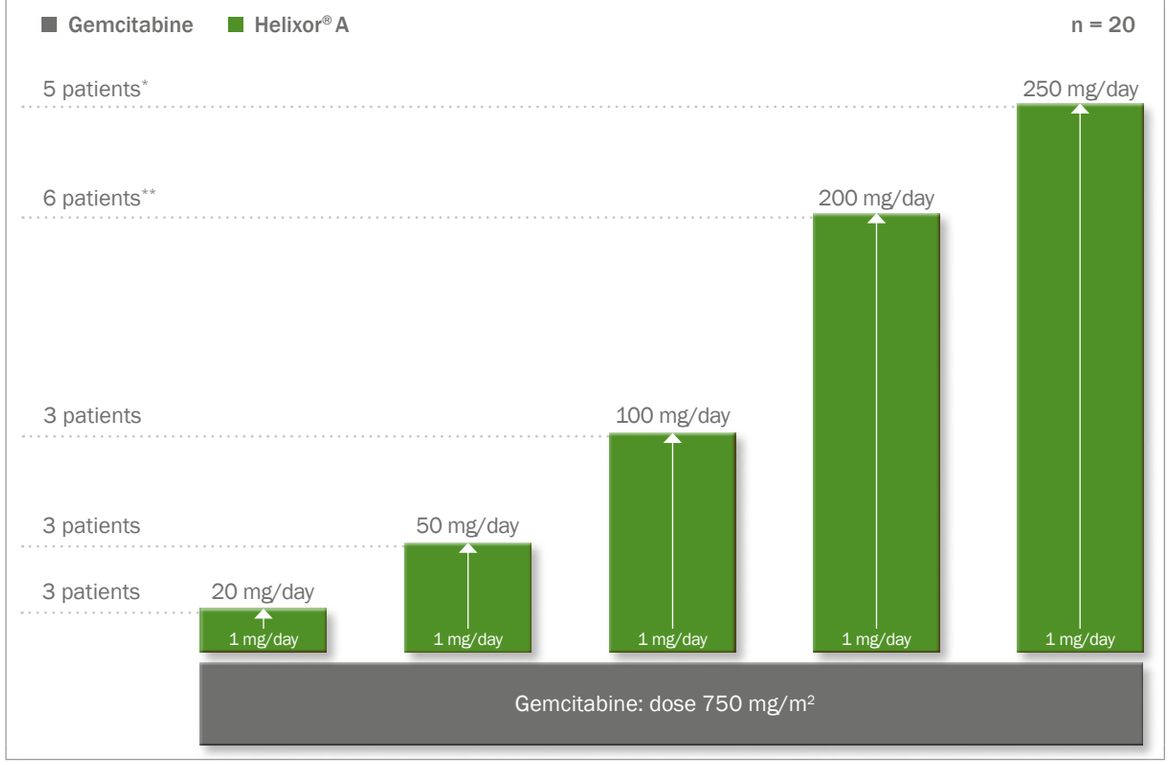
During **stage I** of the study, all patients received 750 mg/m^2 gemcitabine on days 1 and 8 of each three-week cycle (3 cycles = 9 weeks). From week 2, patients received rapidly increasing doses of Helixor® A starting at 1 mg on day 1. Each of the 5 patient groups with 3 patients had different target doses (20, 50, 100, 200, 250 mg/day). Dropouts were substituted.

During **stage II** of the study, all patients received 250 mg Helixor® A as maintenance dose (rapid increase from 1 mg on day 1). Concomitantly, patients received gemcitabine (on days 1 and 8 of each cycle). Starting at 900 mg/m^2, the dose was increased by 20 % increments. Dropouts were substituted. The maximum tolerated dose (MTD) of gemcitabine in combination with Helixor® A was 1,300 mg/m^2. Three dose-limiting toxicities (DLT) occurred at a dose of 1,560 mg/m^2.

Helixor® A did not affect the pharmacokinetics of gemcitabine. The dose-dependent increase in neutrophils in stage I of the study and the determined plasma cytokine concentrations indicate that immunocompetence is retained. The good tolerability of gemcitabine achieved through concomitant Helixor® A therapy was, however, not achieved at the expense of efficacy. The observed partial remission rate of 6 % equals the usual effect of gemcitabine monotherapy in a comparable patient population. Highly remarkable is the stabilization of disease in 42 % of the patients.[24]

Pharmacokinetics of gemcitabine not affected by Helixor® A.
Better tolerability of gemcitabine under Helixor® A treatment. As a result, 30 % higher dose of the cytostatic agent possible. This suggests higher therapy efficacy.

Study stage I: Helixor® A target dose escalation – examination of the tolerability of Helixor® A in combination with gemcitabine



Study stage II: gemcitabine dose escalation – determination of the maximum tolerated dose of gemcitabine in combination with Helixor® A

* incl. 2 dropouts, ** incl. 3 dropouts, *** incl. 1 dropout

Verified improvement of quality of life

In the **pivotal study of EBM level Ib,** patients were treated with standard polychemotherapy. Additionally, the verum group received Helixor® A, the control group Lentinan.*

Study aims	Influence of Helixor® on the quality of life of cancer patients and on the side effects of chemotherapy compared to Lentinan (immunostimulating, injectable basidiomycetes preparation) Drug safety of Helixor®
Indications	Non-small cell lung cancer, breast and ovarian cancer
Study design	Multicentric (3), prospective, randomized, open-label
Patients	233 patients receiving standard chemotherapy Verum group: additional Helixor® A 3x/week SC progressive dose escalation 1 mg → 200 mg Control group: additional Lentinan 4 mg daily IM
Authors	Piao BK, Wang YX, Xie GR, Mansmann U, Matthes H, Beuth J, Lin HS

Quality of life was assessed using 3 validated questionnaires and indices.

The **KPI**** is a physician rating scale for assessing patient activity on a 11-step scale from 100 % (fully active without restriction) to 10 % (patient is moribund) or 0 % (= dead). In this case, changes before/after therapy were rated as “improvement”, “unchanged” or “deterioration”. The percentage of patients showing improvement is provided.

With the **TCM Score***, 5 quality of life dimensions (fatigue, insomnia, loss of appetite and nausea/vomiting) were individually assessed by the physician, each on a scale from 0 (= “none”) to 3 (= “serious”). The 5 single values were summarized to a total score (TCM Score). Accordingly, a negative difference corresponds with improvement.

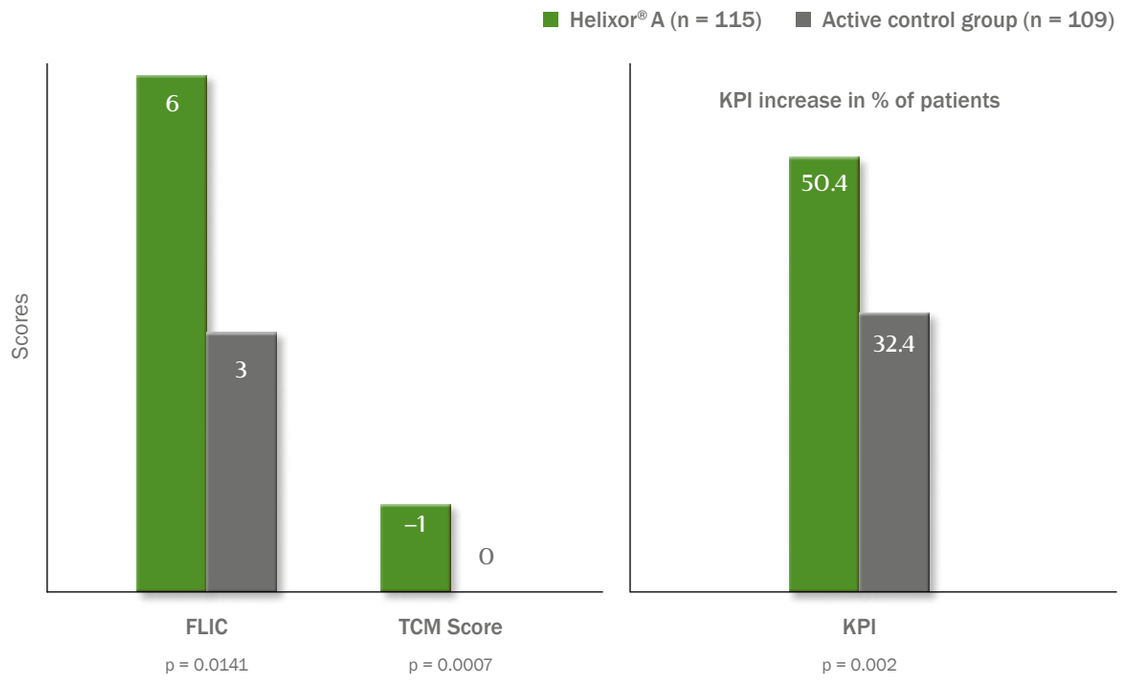
FLIC** is a questionnaire containing 22 single questions, which are answered by the patient. Each question has a continuous scale ranging from 1 to 7. From these individual answers, a total score can be generated (only these were published). The results for the individual questions are attributable in total to 6 single scales (social and mental well-being, physical well-being/activity, cancer-related burden, pain, nausea/vomiting).

A group comparison was conducted of adverse reactions associated with side effects of the chemotherapy to evaluate the influence of mistletoe treatment on how well chemotherapy was tolerated. Those patients additionally treated with Helixor® A showed an improved quality of life which was statistically significant (p = 0.002/0.0007/0.0141) and a better tolerability of their chemotherapy. Improvement was mainly seen with fatigue, insomnia, loss of appetite and nausea.[26]

Significantly improved quality of life with complementary Helixor® therapy compared to control. Significantly less side effects of chemotherapy. Good tolerability and low adverse reactions rate of Helixor® A.

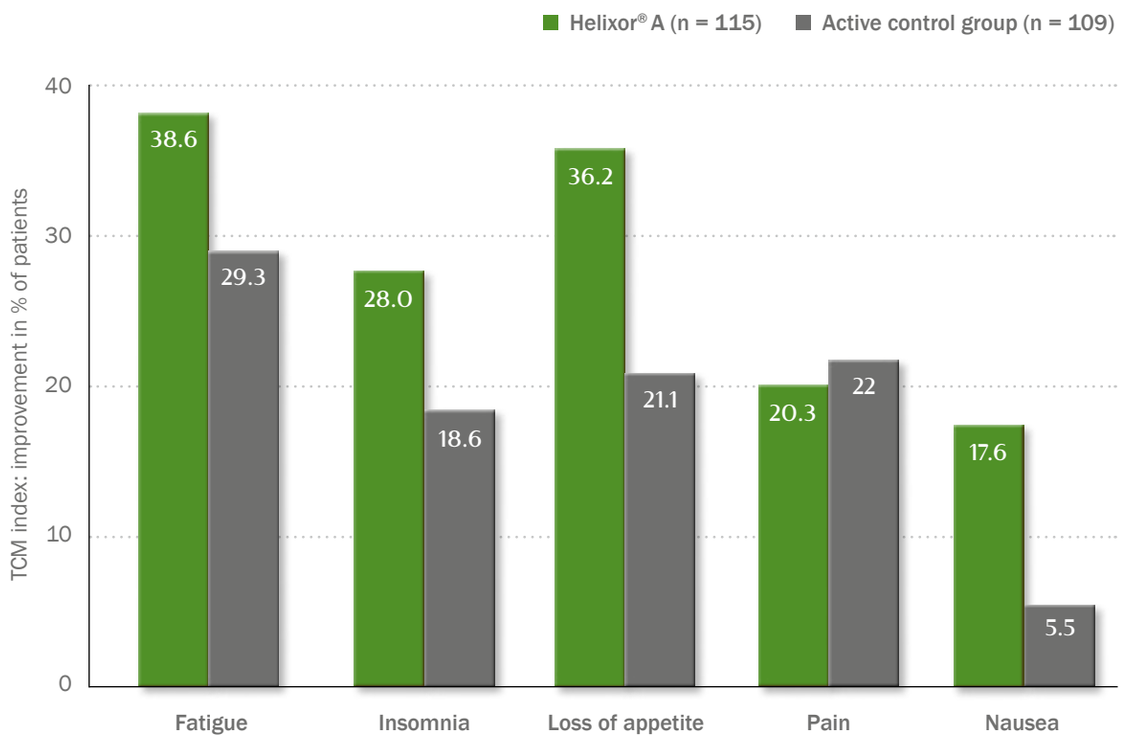
* Immunostimulant/standard oncological supportive medication in China/Japan with verified efficacy on quality of life,
** Karnofsky Performance Index, ***“Traditional Chinese Medicine” Score, **** Functional Living Index: Cancer

Significant improvement of quality of life as compared to active control group in breast, ovarian and lung cancer patients



FLIC = Functional Living Index: Cancer **TCM Score** = Traditional Chinese Medicine Score **KPI** = Karnofsky Performance Index

Improvement in individual dimensions of quality of life in breast, ovarian and lung cancer patients



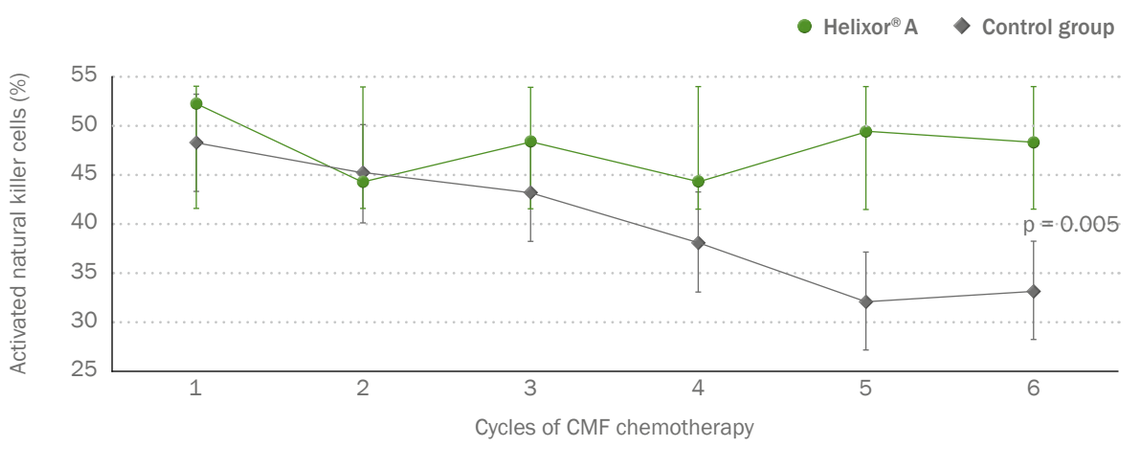
Stimulation of the body's defenses

The prospective, randomized double blind study included 20 evaluable female patients with breast cancer of stage I and II, receiving 6 cycles of an adjuvant CMF chemotherapy and radiotherapy in a sandwich scheme.

Study aim	Feasibility of a double blind study Is there indication of a better tolerability of chemotherapy with Helixor® A?
Indications	Breast cancer (stage I and II)
Study design	Prospective, randomized double blind pilot study
Patients	20 female patients during CMF chemotherapy and radiotherapy (sandwich scheme) Verum group: CMF plus Helixor® A 3x/week 1 amp. SC at individually adjusted dosage (stepwise dose escalation 1 mg ⟶ max. 100 mg) Control group: CMF plus placebo (0.9 % NaCl 3x/week 1 ml SC)
Authors	Auerbach L, Dostal V, Václavik-Fleck I, Kubista E, Rosenberger A, Rieger S, et al.

From cycle 4, women who were additionally treated with Helixor® A showed a significantly higher number of activated natural killer cells compared to the placebo group (p = 0.005). Also shown was a stabilization of activated NK cells (in %) under mistletoe therapy, whereas in the control group there was a significant decrease (p = 0.001).

Significantly higher number of activated natural killer cells (concomitant therapy with Helixor® A in breast cancer patients)



In addition, the increase in sister chromatid exchanges in lymphocytes of patients was considerably lower in the Helixor® group during chemotherapy, which suggests a DNA-protective effect in favor of Helixor® A.[1]

Improved tolerability of chemotherapy through Helixor® A. Significantly higher number of activated natural killer cells. DNA-protective effect of Helixor® A.

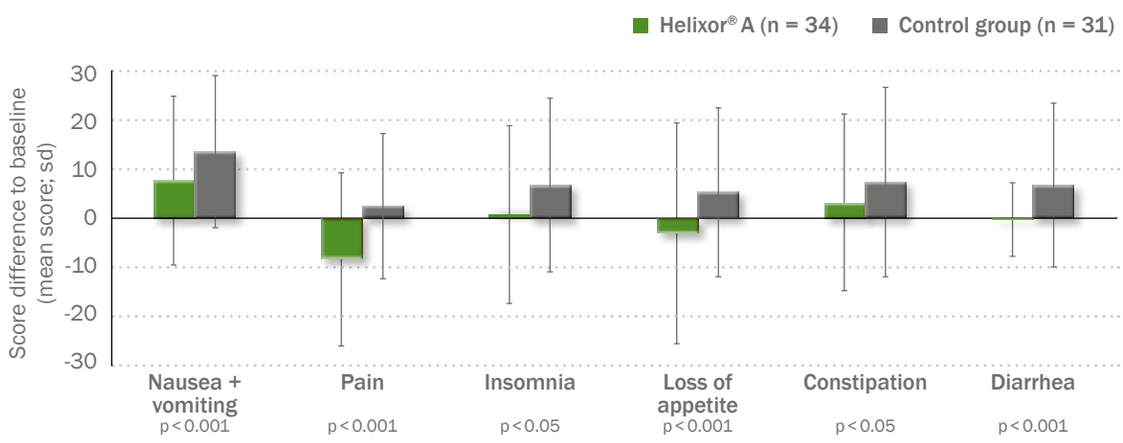
Improved quality of life during chemotherapy

The study conducted in compliance with GCP assessed the postoperative quality of life of 65 female breast cancer patients treated with CAF (cyclophosphamide, adriamycin, 5-FU).

Study aim	Evaluation of the influence of concomitant therapy with Helixor® A on quality of life and neutropenia
Indications	Breast cancer
Study design	Prospective, randomized open-label pilot study
Patients	65 patients after surgery ($T_{1-3}N_{0-2}M_0$) during chemotherapy (6 cycles CAF) Verum group (34 female patients): CAF plus Helixor® A 3x/week SC (dose escalation from 1 mg ⟶ max. 200 mg) Control group (31 female patients): CAF alone
Authors	Tröger W, Ždrale Z, Tišma N, Matijašević M

Mistletoe therapy induced considerable improvement of the patient's quality of life: 10 of the 15 dimensions of the EORTC QLQ-C30 questionnaire, as measure of the quality of life, showed significant improvement: role, social, emotional and cognitive function, insomnia, pain, diarrhea, constipation, loss of appetite and nausea/vomiting. These improvements were clinically relevant for 8 of the 10 parameters (difference of > 5 points in the EORTC QLQ-C30 scores between verum and control group). In 4 further dimensions there was a trend towards improvement.

Improvement in EORTC symptom scores during chemotherapy (concomitant therapy with Helixor® A in breast cancer patients)



Moreover, neutropenia was less frequent in the Helixor® group (21 vs. 26 %) and there were fewer delays in performance of chemotherapy cycles (1.3 vs. 5.5 %, p = 0.0567).[42]

Proven reduction of defined symptoms through concomitant Helixor® A therapy.

Through these studies, earlier results regarding improved tolerability of chemotherapy with concomitant Helixor® therapy have received unequivocal confirmation.

As early as 1985, a similar effect could be shown in a **prospective, randomized pilot study** on the influence of Helixor® treatment. **44 patients with inoperable ovarian cancer, or squamous cell carcinoma of the lung or of the head and neck,** received a combination treatment comprising radiotherapy and an aggressive chemotherapy (ifosfamide, cisplatin).

Patients additionally receiving Helixor® had significantly less nausea ($p = 0.005$), vomiting ($p = 0.09$) and tumor pain ($p = 0.04$). The Karnofsky index showed significant improvement in the Helixor® group ($p = 0.001$). Leukopoiesis also resolved significantly ($p = 0.003$).

Consequently, the full chemotherapy dose could be administered to the Helixor® group as scheduled more often. This could also explain the higher remission rate in the Helixor® group (78.2 % vs. 61.9 %, not significant).[23]

Overall, results from over 25 years of research have proven the efficacy of supportive Helixor® therapy combined with adjuvant and palliative chemotherapy.

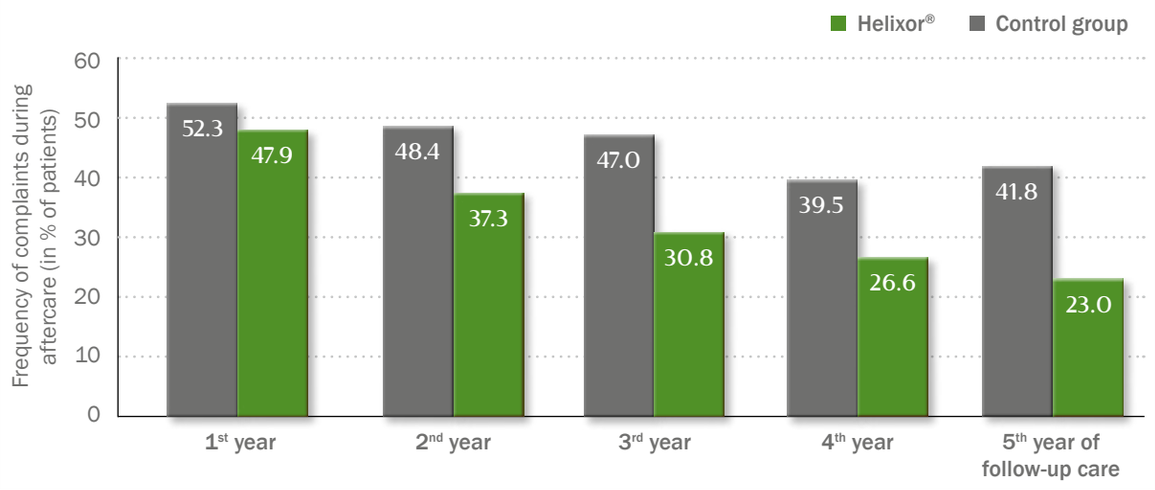
Positive effect on quality of life during follow-up

In a pharmacoepidemiological **long-term study** the frequency of disease- and therapy-associated symptoms was recorded during follow-up in **patients with primary breast cancer** after completed oncological standard therapy.

Study aim	Comparison of disease- and therapy-related signs and symptoms, tolerability of the conventional therapy and of mistletoe therapy
Indications	Breast cancer (stage I – III)
Study design	Multicenter, controlled, pharmacoepidemiological GEP-compliant study
Patients	741 patients, S/P R0 resection and adjuvant chemo- and/or radiotherapy Median follow-up: 4.35 years Mistletoe therapy with Helixor® A, M or P in all years of follow-up: n = 167, without mistletoe therapy: n = 514, changeovers: n = 60
Authors	Beuth J, Schneider B, Schierholz JM

Symptom frequency was significantly lower in patients receiving Helixor® than in the control group without mistletoe therapy ($p < 0.001$). In particular, the incidence of pain, fatigue and mucositis decreased.

Significant reduction of complaints with Helixor® A in follow-up care of breast cancer patients (from 2nd year of treatment)



During the 5-year treatment period, the benefit of mistletoe therapy increased markedly from year to year.[2]

Even after completion of primary therapy, the positive effect of Helixor® on the quality of life of cancer patients continued.

Indication of a possible prolongation of survival time

Since first clinical trials on complementary Helixor® therapy also indicated a possible prolongation of survival time,[3,4,6–11,27,28] several retrospective analyses of mistletoe-treated patients were conducted at the Community Hospital Herdecke additionally.

Retrospective analyses at the Community Hospital Herdecke	
Malignant lymphoma and chronic leukemia	Of 237 evaluable patients, those who had additionally received mistletoe extract showed a longer median survival (11.4 years) compared to patients without mistletoe therapy (8.6 years). Furthermore, results again confirmed indications of an improved quality of life in patients treated with mistletoe products. The outcome of this study, therefore, does not confirm frequently expressed concerns that mistletoe therapy may adversely affect the course of hematological malignancies.[37]
Breast cancer	An analysis including 1,246 female patients with operated breast cancer, who had been treated with adjuvant mistletoe therapy, revealed 73.3 % with a 10-year survival rate compared to 54 % in the Munich tumor registry. The more advanced the tumor stage, the greater the benefit of mistletoe therapy: stage II: 71.6 vs. 65 %, stage III: 55.6 vs. 30 %.[36]
Colorectal cancer	476 patients with operated colorectal carcinoma of all stages, who received mistletoe therapy, had significantly longer survival than in 8,151 patients from the Saarland cancer registry, Germany ($p < 0.0001$): Median survival was 59 vs. 38 months, the 5-year survival rate 48.9 vs. 40.3 % and the 10-year survival rate 42.7 vs. 27.2 %.[35]
Melanoma	For 94 of 284 patients included in an analysis, an evaluable complete data set was available for assessment. In 66 patients treatment with mistletoe therapy was documented. Though the mistletoe group in which 33.3 % had metastases at baseline – as against 0 % metastases in the control groups – had a markedly worse prognosis, it showed similar survival rates compared to external control groups in the literature (5-year survival 80 %, 10-year survival 68 %).[38]

Retrospective analyses at the Community Hospital Herdecke	
Various entities	A retrospective analysis from 2009 included all patients, who had received treatment at the Community Hospital Herdecke's tumor outpatient center over a period of 20 years. For the assessment of overall survival, 157 patients with breast cancer, 323 with colorectal cancer, 221 with malignant lymphomas, 52 with melanoma and 22 with pancreatic cancer, all who had received mistletoe therapy, were evaluated in comparison with patient data from the Saarland epidemiological cancer registry. In all five tumor entities, the survival probability for patients treated with mistletoe was remarkably higher ($p < 0.001$ to 0.022). After stratification into prognostically homogenous subgroups within the tumor entities using the CART method, survival was found to be significantly longer in all breast cancer and lymphoma subgroups, melanoma patients over 50 years of age, stage I and II, as well as all colorectal cancer subgroups, except for patients under 68 years of age in stage I and II.[34]

Earlier indications of longer survival times through Helixor® therapy were also supported by these analyses. However, due to their limitation to one center and the retrospective approach of the studies, transferability of the results to other centers and to the current oncological setting is difficult and further research is required. A comparison with epidemiological data from registries is also problematic.

Whether improvement of quality of life with Helixor® also has an influence on survival time, as Temel et al. 2010 showed for intensive palliative care in metastatic lung cancer,[40] has not been studied.

Meanwhile, however, a study on another mistletoe product in a large group of patients with pancreatic cancer, was able to demonstrate a significant prolongation of overall survival through mistletoe therapy.[41]

Further scientific publications

Scientific acceptance of a therapy, besides relying on the number and quality of clinical studies, also depends on the total number of scientific publications.

Currently, there are more than 250 publications available about Helixor®, including 31 doctoral and diploma theses and two postdoctoral theses (habilitation), which were conducted or written, respectively, at German universities, and over 60 peer-reviewed papers published in renowned international scientific journals.

All preclinical and clinical research results on mistletoe therapy are summarized and discussed critically in the German **standard scientific work** "Die Mistel in der Onkologie – Fakten und konzeptionelle Grundlagen" (The mistletoe in oncology – facts and conceptual basic principles). Here, the specific characteristics of the mistletoe products are listed in tables, taking an overall positive view of most important research results as well as several case studies and experience reports.[17]

Positive view of Helixor® therapy in numerous reviews and summaries

- In 5 critical summaries[13, 15, 18 – 20] on clinical studies on mistletoe therapy, 11 of the reviewed Helixor® studies were rated as valid.[1, 3, 4, 6 – 9, 23, 24, 26, 42]
- In one review of controlled clinical studies on the influence of mistletoe therapy on the quality of life, the authors drew the following conclusion: In clinical studies as well as in daily practice mistletoe products demonstrate a **positive influence on the quality of life** (**primarily fatigue**) and **reduction in the side effects of conventional therapies** (**chemotherapy, radiotherapy**).[19]
- In one review of the influence of mistletoe products on breast cancer or gynecological tumors, strongest evidence was provided regarding improvement of the quality of life and **tolerability of standard cancer treatment.** Tumor regression, however, could not be documented for usual low-dosed subcutaneous mistletoe therapy, but only for high-dosed and local administration.[15]
- On the basis of the reviewed studies, the Cochrane review from 2008[13] evaluating the evidence for the use of mistletoe products in addition to chemotherapy also reaches a positive conclusion regarding their efficacy, when only in female breast cancer patients: 14 of the 16 randomized studies of qualitatively high value demonstrated **improved quality of life** under mistletoe therapy. A further 6 of 13 studies showed a **beneficial influence on survival.** This review included 4 Helixor® studies[1, 7, 23, 26] which complied with the strict criteria of the Cochrane Collaboration.

Scientific Findings on Drug Safety

In a comprehensive analysis of the effect of mistletoe products on the immune system and other safety parameters, which included not only results from clinical studies but also all available findings from animal studies and from cell culture, the authors could find no indications of immunosuppressive effects (Kienle et al 2011).[16] Only dose-related flu-like symptoms, fever, inflammatory reactions at the injection site and various other mild unspecific effects were described. Allergic reactions may also occur occasionally.

The authors of the Cochrane review of the randomized mistletoe studies[13] also reached the conclusion that, depending on the dose mistletoe products cause only few symptoms and are generally well tolerated. These observations from clinical studies have been confirmed by experiences with adverse reactions in the practical use of Helixor®, as collected and presented in periodic safety update reports (PSURs). The reports reflect a 20-year period of Helixor® administration.

An evaluation of data in the “Netzwerk Onkologie” (network oncology) databases also provides a detailed description of the tolerability of mistletoe products.[33] The network is a consortium of hospitals, out-patient centers and private practices, with the aim to obtain a structured collection of all diagnostic tumor data and therapies conducted in the course of a tumor disease since 2005.

This analysis, published in 2014, also includes the data of 323 patients, who received mistletoe therapy with Helixor®. Overall, 162 (8.4 %) of the 1,923 assessed patients experienced 264 adverse drug reactions (ADRs). In most of the cases, their course was mild (50.8 %) or moderate (45.1 %), only 4.2 % reported a more severe course of symptoms. Serious adverse drug reactions did not occur.

In line with the analysis by Kienle et al.[16] the majority of cases (92.4 %) were excessive local reactions > 5 cm, elevated body temperature/fever and flu-like symptoms. The remaining ADRs included a few cases of headache, allergic symptoms such as rash, generalized itching or urticaria, and also several isolated observations. No specific risk factors could be identified. The frequency of ADRs was dose-related, as expected, however, they were less frequent when the mistletoe therapy was administered in combination with conventional therapy than in monotherapy.

Registration and Approval

Helixor® was registered in the Federal Republic of Germany in 1976 after several years of clinical trials and in February 1982 obtained approval in Germany as first mistletoe product for subcutaneous administration in accordance with the German Drug Law (AMG). Besides in Germany, Helixor® mistletoe products are also approved in Austria, Switzerland, Luxemburg, Sweden, Latvia, Lithuania, Macedonia, Korea, Russia, Chile, Peru and Canada.

Last, but not least, acceptance of a therapy in the scientific world is also demonstrated by the **frequency of its use.** Mistletoe products are still among the 2,000 most prescribed medicinal products in Germany.[30]

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