Integrative Cancer Therapies
9(2) 142–157

DOI: 10.1177/1534735410369673
http://ict.sagepub.com
SAGE

Influence of *Viscum album* L (European Mistletoe) Extracts on Quality of Life in Cancer Patients: A Systematic Review of Controlled Clinical Studies

Gunver S. Kienle, MD[1], and Helmut Kiene, MD[1]

Abstract

Objective. To evaluate controlled clinical studies on the efficacy and effectiveness of *Viscum album* for quality of life (QoL) in cancer. *Materials and methods*. The authors conducted a search of 7 electronic databases and reference lists and had extensive consultations with experts. They carried out a criteria-based assessment of methodological study quality. *Results*. The authors identified 26 randomized controlled trials (RCTs) and 10 non-RCTs that investigated the influence of *V album* extracts (VAEs) on QoL in malignant diseases; 26 studies assessed patient-reported QoL. Questionnaires were mostly well established and validated. Half of the studies investigated VAEs concomitant with chemotherapy, radiotherapy, or surgery. Some studies were well designed, whereas others had minor or major methodological weaknesses. Among the 26 RCTs, 22 reported a QoL benefit, 3 indicated no difference, and 1 did not report any result. All the non-RCTs reported a QoL benefit. Of the studies with higher methodological quality, most reported a benefit, whereas 1 found no difference. Improvements were mainly in regard to coping, fatigue, sleep, exhaustion, energy, nausea, vomiting, appetite, depression, anxiety, ability to work, and emotional and functional well-being in general and, less consistently, in regard to pain, diarrhea, general performance, and side effects of conventional treatments. VAEs were well tolerated. *Conclusions*. VAEs seem to have an impact on QoL and reduction of side effects of conventional therapies (chemotherapy, radiation) in experimental trials as well as in routine daily application. The influence on fatigue especially should be investigated further.

Keywords

clinical trials, quality of life, complementary therapies, herbal medicine, *Viscum album*, mistletoe, neoplasms

Review: Background

Cancer patients often use herbal extracts in addition to well-established cancer treatments.[1] *Viscum album* L extracts (VAEs) are among the most frequently prescribed herbal extracts, especially in German-speaking countries[1-5] and are also currently under investigation at the National Center for Complementary and Alternative Medicine (NCCAM).[6]

V album L, also known as European mistletoe (not to be confused with *Phoradendron*, the "American mistletoe") is a semiparasitic shrub that grows on other trees and has been used in cancer treatment for about 80 years. Its extracts contain a variety of biologically active compounds. The most thoroughly investigated compounds are the mistletoe lectins (ML I, II, and III). MLs consist of 2 polypeptide chains: a carbohydrate-binding B-chain that can bind to cell surface receptors, which enables the protein to enter the cell,[7-9] and the catalytic A-chain, which, because of its ribosome-inactivating properties, can subsequently inhibit protein synthesis by removing an adenine residue from the 28S RNA of the 60S subunit of the ribosome.[7] Other pharmacologically relevant VAE compounds are viscotoxins and other low-molecular-weight proteins, VisalbCBA (*V album* chitin-binding agglutinin),[10] oligosaccharides and polysaccharides,[11,12] flavonoids,[13] vesicles,[14] triterpene acids,[15] and others.[16,17] Whole VAEs as well as several of the compounds are cytotoxic, and the MLs in particular have strong apoptosis-inducing

[1]Institute for Applied Epistemology and Medical Methodology, Freiburg, Germany

Corresponding Author:
Gunver S. Kienle, Institute for Applied Epistemology and Medical Methodology, Zechenweg 6, D-79111 Freiburg, Germany
Email: gunver.kienle@ifaemm.de

effects.[18-20] MLs also display cytotoxic effects on multidrug-resistant cancer cells (eg, *MDR*+ colon cancer cells[21]) and enhance the cytotoxicity of anticancer drugs.[22,23] In mononuclear cells, VAEs also possess DNA-stabilizing properties. VAE and its compounds stimulate the immune system (in vivo and in vitro activation of monocytes/macrophages, granulocytes, natural killer cells, T-cells, dendritic cells, and induction of a variety of cytokines such as IL-1 [interleukin-1], IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, GM-CSF [granulocyte-macrophage colony-stimulating factor], TNF-α [tumor necrosis factor α], IFN-γ [interferon γ]; for overviews see Kienle and Kiene[16] and Büssing[17]). The cytotoxicity of human natural and lymphokine-activated killer cells, for instance, can be markedly enhanced in vitro by VAE rhamnogalacturonans, which bridge these killer cells with natural-killer-sensitive or -insensitive tumor cells.[24,25] Furthermore, VAEs seem to interfere with tumoral angiogenesis.[26,27] Injected into tumor-bearing animals, VAEs and several of their compounds (MLs, a 5 kDa protein not specified further, protein complexes isolated by Vester and colleagues, oligosaccharides) display growth-inhibiting and tumor-reducing effects.[16,17] Besides cytotoxicity, immune modulation, and DNA stabilization, VAEs can also enhance endorphins in vivo.[16,17]

Mistletoe treatment for cancer was introduced in the context of anthroposophical medicine, a complementary medical method.[28] Anthroposophical mistletoe preparations—abnobaVISCUM, Helixor, Iscador (labeled as "Iscar" in the United States), Iscucin, and Isorel—are extracts from defined parts of *V album*, that is, fresh leafy shoots and berries. These preparations are available from different host trees such as oak, apple, pine, and others. The harvesting procedure is standardized, and the juices from summer and winter harvests are mixed together. Route of application and dosage vary individually, depending on the patient's reaction and the stage of the disease. Nonanthroposophical VAEs—Cefalektin, Eurixor, and Lektinol—are harvested in winter from poplars; they are dosed according to mistletoe lectin content (ranging from 1 ng/kg up to 15 ng/kg bodyweight) on the premise that mistletoe lectin is the main active ingredient.[17]

Various clinical studies have assessed safety and possible effects on tumor growth, survival, and quality of life (QoL). Regarding antitumor and survival-prolonging effects, conclusions of systematic reviews of these studies were inconsistent, whereas possible benefits regarding QoL for cancer patients were mentioned in reviews that also included recent trials. These reviews, however, present only little detail on QoL; furthermore, they are either confined to certain preparations[29,30] or cancer types[31] or are otherwise incomplete or outdated.[32-37]

Clinical research on cancer treatment used to concentrate on outcomes like survival and tumor remission. For decades, subjective well-being was regarded as of minor importance, too complex and fuzzy and not tangible enough for straightforward scientific assessment.[38] This attitude has changed considerably. The substantial suffering of cancer patients has been widely realized, and improvement in how patients feel while having the disease became an ethical imperative. Improvement of health-related QoL is today acknowledged as an important therapeutic goal and a well-established end point in clinical trials. A multitude of generic or specific instruments have been designed to assess different aspects of subjective well-being and function.[39,40] Still, adequate improvement in QoL in cancer patients and the relief of their multifaceted suffering remains a challenge. All options should therefore be carefully scrutinized for potential benefits.

QoL is a complex concept, covering a variety of areas such as general aspects of well-being; physical, emotional, and social functioning; general condition; disease symptoms; and side effects of treatment. Therefore, a closer, detailed, and differentiating critical analysis of the potential effects of VAE on these QoL aspects is of major clinical importance. For this reason, clinical studies were critically analyzed here to answer the following questions: Do controlled clinical studies provide evidence for the effectiveness of VAE in regard to QoL? If yes, which QoL aspects respond in particular? How far reaching is the clinical significance?

Material and Methods

Search Strategy

We used a systematic process to search the following databases for clinical trials: AMED, BIOSIS Previews, CAMbase, Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, The NHS Economic Evaluation Database, Health Technology Assessment Database), Embase, MEDLINE/PreMEDLINE, NLM Gateway, and private databases. This was done from inception of these databases to October 2009 using the terms (MISTLETOE OR VISCUM? OR MISTEL? OR ISCADOR? OR ISCAR OR HELIXOR OR ABNOBA? OR ISCUCIN OR ISOREL OR VISOREL OR ?SOREL OR EURIXOR OR LEKTINOL) AND (STUDY? OR STUDIE? OR TRIAL OR EVALUAT? OR RANDOM? OR INVESTIG? OR COHORT? OR KOHORT?) The reference list from each potentially eligible study, relevant review article, and textbook was checked, and experts in the field and manufacturers of VAE preparations were contacted for additional reports. Potential clinical studies were individually checked for QoL outcomes.

Definition of QoL

In spite of the importance of QoL for cancer patients, there is no consensus regarding its definition. For this review, we chose a broad, pragmatic definition that covers all aspects of how patients feel and function during the disease and its

treatment, including psychosomatic self-regulation, subjective well-being, disease symptoms, performance status (Karnofsky Performance Status Scale, KPS), undesirable experiences associated with the use of chemotherapy or radiotherapy (summarized here as adverse drug reactions [ADRs]), and treatment symptoms. We included QoL assessed by patients or physicians, using multidimensional or unidimensional questionnaires as well as global ratings.

Selection

The following selection criteria were used for inclusion of studies in the analysis: (1) prospective randomized or nonrandomized controlled clinical study or pharmacoepidemiological cohort study; (2) including a control group; (3) study population with cancer; (4) intervention group treated with VAE preparation; (5) QoL outcome; (6) completion of study; (7) published or unpublished. Studies were excluded if they only measured toxicity or tolerability (phase I trial), only measured stimulation of immunological parameters, or were not conducted on cancer patients. There were no restrictions on language.

Validity Assessment and Data Abstraction

Criteria-based analysis was performed on the selected studies to assess their methodological quality. Regarding general methodological strength of the studies, criteria were adapted from the National Health Service Centre for Reviews and Dissemination[41] and from criteria for good methodology as already applied in earlier reviews on VAE trials.[29,33,42] Analyses were performed independently by 2 reviewers. There were no major differences in study assessment; disagreements were resolved by discussion.

The QoL assessment methodology was evaluated using criteria adapted from the "Minimum Standard Checklist for Evaluating HRQoL Outcomes in Cancer Clinical Trials."[43] The data were abstracted by one reviewer and checked by the second reviewer. When necessary, primary authors of the trials were contacted for additional information.

Results

The primary search yielded more than a thousand references. After deleting all articles that did not meet the inclusion criteria (eg, no clinical study, laboratory research, reviews, opinions, studies not on cancer or not on QoL, only investigating complex treatment regimes, only descriptive studies) and after deleting double citations and combining articles referring to the same study, 36 studies were left that met the inclusion criteria. Of these, 26 were randomized controlled trials (RCTs), and 10 were nonrandomized controlled studies (non-RCTs). One further RCT (on Lektinol and breast cancer, by Schwiersch et al) might have met the inclusion criteria but was unpublished and unavailable.

Characteristics of Included Trials

Table 1 shows the characteristics of the trials. Settings of the trials were mainly academic hospitals, large community hospitals, and specialized cancer hospitals or outpatient departments. Most of the studies were conducted in Germany, the others in Austria, Switzerland, Italy, Serbia, Russia, Bulgaria, Ukraine, Romania, China, and South Korea. 14 trials were conducted in 1 center and 22 in more than 1 center. Most RCTs and 4 non-RCTs were conducted in conventional medical settings; 3 RCTs and 5 non-RCTs included hospitals or outpatient clinics that also provide complementary medicine methods; 1 was unclear in this regard.

A total of 26 RCTs included 3058 patients, and 10 non-RCTs included 4996 patients (4012 of the latter were part of 5 pharmacoepidemiological cohort studies). Cancer sites and types studied were the following: breast (15), ovary (4), cervix uteri (2), corpus uteri (2), colorectal (3), pancreas (1), gastrointestinal (2), lung (3), head and neck (2), melanoma (2), glioma (1), osteosarcoma (1), various (1), malignant pleural effusion (1). Stages ranged from early detected to advanced disease. Of these studies, 32 had 2 arms, and 4 trials had 3 or more arms; 4 of the RCTs were double blind,[44-47] 3 other RCTs had an open placebo or pseudoplacebo treatment in the control group (placebo,[48] vitamin B,[49] or lentinan[50]), and 2 RCTs compared VAE with chemotherapy.[51,52] The control groups of the other trials had received no additional therapy.

Combinations of VAEs and conventional cancer treatment were investigated by 22 studies: VAEs were applied concomitantly with chemotherapy in 10 studies, with radiotherapy in 2 studies, with both in 7 studies, versus chemotherapy in 2 studies, and perioperatively in 1 study. In the remaining 14 studies, VAEs were investigated independently of concomitant conventional cancer treatment; nevertheless, these patients received standard cancer care when appropriate. VAEs were injected subcutaneously except in 2 studies using intravenous infusion or intrapleural instillation.

Length of follow-up regarding QoL was 3 months or less in 8 studies, 4 months to 1 year in 18 studies, more than 1 year in 2 studies, and not reported in 8 studies. Frequency of assessment after baseline was once in 13 studies, twice in 1 study, repeatedly in 15 studies, and not specified in 7 studies. In all, 30 of the studies are published, 5 are available only as abstracts or poster presentations, 1 is not published.

Methodological Quality

Methodological quality of the 36 studies varied (Table 2); some of the studies were well designed, whereas others had methodological weaknesses or insufficient reporting. Also, 26 studies had randomized treatment allocation; in 4 of these trials, patients and physicians were blinded to treatment application; 5 additional studies had an open placebo, pseudoplacebo, or active treatment control, and 15 had no comparative

Table 1. Characteristics of the 36 Included VAE Studies

Item	Description	Number of Studies	Percentage
Year of publication	1980-1990	1	3
	1991-2000	5	14
	2001-2009	30	83
Publication	Medical, scientific journal	27	75
	Abstract, poster presentation	5	14
	Book, book chapter	3	8
	Unpublished	1	3
Sample size	>201	13	36
	101-200	2	6
	51-100	10	28
	≤50	11	31
Cancer type	Breast	15	42
	Other gynecological	8	22
	Gastrointestinal	7	19
	Lung, head & neck	5	14
	Others	6	17
Stage	Local disease, no distant metastases	21	58
	Advanced, distant metastases	8	22
	Both	6	17
	Unclear	1	3
Mistletoe preparation[a]	Iscador	21	58
	Helixor	6	17
	Eurixor	5	14
	Isorel	2	6
	Lektinol	2	6
	abnobaVISCUM	1	3
Treatment of control group	Placebo	5	14
	Pseudoplacebo or active treatment	4	11
	Standard treatment only	27	75
Investigating QoL concomitant with conventional cancer treatment	Total	20	56
	Chemotherapy	17	47
	Radiotherapy	9	25
	Surgery	1	3
Outcomes measured besides QoL	Survival	21	58
	Progression-free survival	11	31
	Tumor behavior	6	17

NOTE: VAE = Viscum album L extract; QoL = quality of life.
[a]One study investigated both Iscador and Helixor.

additional treatment. Of the 10 nonrandomized studies, 4 prospectively matched all patients for a series of relevant patient and disease characteristics[53-55]; 1 did not conduct any adjustment for baseline imbalances[56]; 5 were retrolective pharmacoepidemiological observational cohort studies: of these 4 were adjusted for confounder effects with a multivariate analysis[57-61] and 1 with propensity scores.[62]

QoL was the primary outcome in 14 studies. The primary outcomes of the other studies were overall survival, disease-free survival, functional competence of granulocytes, or not specified.

QoL or symptom control was patient-reported in 26 studies; in 1 of these, the questionnaire was filled out in an interview situation as some of the patients were illiterate.[50] Only physician-reported QoL was referred to in 8 studies, with 5 of these studies raising data from patient charts. QoL reporting was unclear in 2 studies.[63,64] In 1 study, the result of several patient-reported questionnaires had been summarized by the physician in a 5-point résumé (QoL index).[48] Patient-reported measurements included well-established QoL questionnaires, most of them designed specifically for cancer patients (see Tables 3-5). Other questionnaires included one on psychosomatic self-regulation and a simple daily analogical QoL report. Physicians reported subjective improvement of QoL, Traditional Chinese Medicine Index, disease- and treatment-associated symptoms, KPS, and ADR. Information from patient charts concerned disease- and treatment-associated symptoms and KPS. Two trials did not specify their QoL instrument.

Of the 36 studies, 2 described an a priori statistical hypothesis for improvement of QoL. Of the 26 studies assessing

Table 2. Methodological Quality of the 36 VAE studies assessing QoL[a]

Methodological Issue	Description	Number of Studies	Percentage
Study type	RCT	26	72
	Non-RCT, pair matching or statistical adjustment for baseline imbalances	4	11
	Non-RCT, no adjustment	1	3
	Retrolective cohort study, statistical adjustment for baseline imbalances	5	14
Blinding of treatment	Blinding	4	11
	Open but placebo or pseudoplacebo or active control	5	14
	Open, no placebo control	27	75
Protection against performance (treatment) bias	Yes	1	3
	Partly	5	14
Primary end points of studies	Specific QoL measurements, including a priori statistical hypothesis	2	6
	QoL in general	12	33
	Overall survival	11	31
	Disease-free survival	3	8
	Granulocyte function, or not specified	7	19
Use of validated QoL questionnaires	Yes	23	64
	Partly validated	1	3
Protection against measurement (detection) bias	Yes	24	67
	Partly	2	6
Protection against attrition (exclusion) bias	Yes	11	31
	Partly	1	3
Well-described intervention, patient characteristics, disease, previous therapy	Yes	13	36
	Partly	16	44
Well-described study design	Yes	16	44
	Partly	13	36
Well-described results	Yes	17	47
	Partly	11	31
Data quality ensured by good clinical/epidemiological practice (GCP/GEP) guidelines, especially by monitoring	Yes	10	28
	Partly	2	6

NOTE: VAE = *Viscum album* L extract; QoL = quality of life; RCT = randomized controlled trial.
[a]For details of assessment see references 29 and 31.

patient-reported QoL with a questionnaire, 24 gave a rationale for using the particular instrument or used a standard questionnaire (eg, EORTC QLQ-C30 [European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Cancer]); 24 of these 26 studies either used a well-established and well-known questionnaire or reported its psychometric properties. All the QoL questionnaires and the investigated symptoms are relevant for cancer patients. In all, 13 of the studies described instrument administration; 14 of the studies gave at least some relevant information regarding baseline compliance; 25 studies reported the timing of the assessment; 7 studies gave details on missing data or had no missing data at all; none of the studies explicitly and in detail addressed the issue of clinical significance from the patient's perspective (over and above statistical significance), except the studies reporting complete disappearance or nonoccurrence of symptoms, thus, implying patient benefit; 22 of the studies discussed their QoL results in general.

We found substantial heterogeneity of the studies in terms of intervention, patient characteristics, clinical diagnosis, measured outcomes, design, methodological quality, and potential positive and negative biases. We therefore regarded quantification of effect size by combining results as unreliable and decided on a nonquantitative synthesis and discussion.

QoL Result

Of the 26 RCTs, 22 reported a QoL benefit for VAE, 2 indicated no difference, 1 had mixed results, and 1 did not present the QoL results. None found a disadvantage for VAE. Of the non-RCTs, all reported a QoL advantage for VAE except one that reported an advantage in global symptoms but a clear

Table 3. Measurement of QoL, Symptom Control and Overall Results of VAE Studies

Measurement, Questionnaire	Advantage		No Advantage		Total
	RCT	Non-RCT	RCT	Non-RCT	
Patient-reported QoL or symptom control					
Self-regulation questionnaire					
Ability to achieve well-being, inner equilibrium, appropriate stimulation, a feeling of competence, a sense of being able to control stressful situations	7	4			11
EORTC QLQ-C30					
Functional Scale (physical, role, cognitive, emotional, social), Symptom Scale (fatigue, pain, nausea/vomiting, appetite), single items (constipation, diarrhea, sleep, dyspnea, financial), Global QoL	3	1	4		8
EORTC QLQ-BR 23 (Breast module)		1	1		2
EORTC QLQ-STO22 (Stomach module)					1[a]
FACT G, FACT V 3.0					
Physical well-being, emotional well-being, functional well-being, well-being relating to social/family life, relation to doctor	2				2
GLQ-8					
Anxious/depressed, nausea/vomiting, numbness or pins and needles, loss of hair, tiredness, appetite, sexual interest, thought of actually having treatment	2				2
Spitzer Uniscale					
Overall quality of life	2				2
Spitzer Quality of Life Index					
Activity, daily living, health, support, outlook	2				2
FLIC					
Physical, psychological, social well-being, nausea, pain	1				1
Global daily analogical QoL report			1		1
Scale of anxiety					
Therapy anxiety scale	2				2
QoL index					
Five-point résumé of (1) well-being scale, (2) list of complaints, (3) list of adjectives, and (4) FLIC	1				1
Rhodes Index					
Nausea, vomiting, and retching			1		1
Physician-reported QoL or symptom control					
Subjective improvement of QoL	1				1
TCM					
General fatigue, insomnia, anorexia, nausea, pain	1				1
KPS	3	2	3		8
Tumor symptoms	1	5	1		7
ADR or other treatment symptoms	8	5	2		15
Others					
QoL-evaluation, Not specified	1				2[a]

NOTE: VAE = *Viscum album* L extract; QoL = quality of life; RCT = randomized controlled trial; ADR = adverse drug reaction; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Cancer; BR = breast; STO = stomach; FACT = Functional Assessment of Cancer Therapy; FLIC = Functional Living Index–Cancer; GLQ = Global Life Quality; KPS = Karnofsky Performance Status Scale; TCM = Traditional Chinese Medicine Index.

[a]Two studies mentioned no results.

disadvantage in the unadjusted occurrence of depression.[60] Details are given in Tables 3 to 5.

Advantage for VAE was found with all QoL questionnaires except with the Rhodes Index (1 study), with a daily analogical QoL report by patients (1 small pilot trial), and with the EORTC QLQ-C30 (plus the BR 23 module in 2 studies), which had mixed results (4 showed benefit and 4 with no difference).

Patient-reported QoL improved in all but 3 studies, one of which was an abstract and presented only little information.[67] Regarding physician-reported QoL, symptom control, ADR, and performance status, a benefit for VAE was found in most but not all studies (Tables 3 to 5).

Of the 4 double-blind RCTs, 3 indicated a significant benefit, whereas a small pilot trial could not find a difference.

Table 4. QoL Results of Studies on VAE Treatment Concomitant With (in 2 Study Versus) Conventional Cancer Treatments (Chemotherapy, Radiotherapy, Surgery)

Author, Year	QoL Measure	Benefit From VAE, *P* Value, Specification of Improvement	No Benefit	Disadvantage
RCTs on VAE concomitant with (in 2 studies versus) chemotherapy				
Eisenbraun, 2009[65]	• EORTC QLQ-C30, STO22; ADR	• EORTC QLQ-C30 sum score ($P < .01$); ADR: reduced incidence of diarrhea	• STO22: no results mentioned	
Longhi et al, 2009[52]	• EORTC QLQ-C30; ADR	• EORTC QLQ-C30; ADR: trend		
Tröger et al, 2009[66]	• EORTC QLQ-C30	• EORTC QLQ-C30: pain ($P = .0003$), diarrhea ($P = .0073$), role ($P = .0008$), insomnia ($P = .0212$), nausea/vomiting ($P = .0438$); trend: emotional ($P = .0686$), social ($P = .0898$), cognitive ($P = .1519$), appetite loss ($P = .0817$), constipation ($P = .1675$)	• EORTC QLQ-C30: remaining 5 dimensions	—
Büssing et al, 2008[67]	• EORTC QLQ-C30, BR 23; Rhodes Index; ADR	• ADR: "significant": nausea (odds ratio 6.0), constipation (odds ratio 4.6), pain (odds ratio 2.7), stomatitis (odds ratio 5.7), appetite (odds ratio 8.2)	• EORTC QLQ-C30, BR 23; Rhodes Index	
Semiglasov et al, 2006[45]	• FACT-G[a] (3 subscales); GLQ-8; Spitzer Uniscale; ADR; KPS	• FACT-G ($P < .0001$): physical well-being ($P < .0001$, especially energy, nausea, trouble meeting needs of family, feeling ill, bothered by side effects of treatment, time in bed); emotional well-being ($P < .0001$, especially feeling sad, feeling nervous, worry that condition is getting worse); functional well-being ($P < .0001$, especially ability to work, work is fulfilling, enjoy life, accept illness, sleep, fun, content with QoL); • GLQ-8 ($P < .0001$): anxious or depressed ($P < .0001$), fatigue/tiredness ($P < .0001$), appetite ($P < .0001$), sexual interest ($P < .0001$), thought of actually having treatment ($P < .0001$), nausea/vomiting ($P < .0001$); numbness ($P = .03$). • Spitzer Uniscale ($P < .0001$)	• GLQ-8: having pain, coping with my illness, worry about dying, loss of hair, numbness or pins and needles; ADR; KPS	—
Piao et al, 2004[50]	• TCM; FLIC; KPS; ADR	• TCM ($P = .0007$): nausea, fatigue, insomnia, anorexia; FLIC ($P = .0141$): especially nausea and pain; KPS ($P = .002$); ADR (P not stated)	• TCM: pain	—
Semiglasov et al, 2004[44]	• GLQ-8[a]; Spitzer Uniscale[a]; EORTC QLQ-C30; ADR	• GLQ-8 ($P = .0035$)[b]: tiredness ($P < .05$), sexual interest ($P < .05$), thought of actually having treatment ($P < .01$); trend: nausea/vomiting, appetite; Spitzer Uniscale ($P = .0021$)	• GLQ-8: anxious or depressed, numbness or pins and needles, loss of hair; EORTC QLQ-C30; ADR	—
Cazacu et al, 2003[64]	• ADR; QoL evaluation	• ADR: 0% versus 19% side effects (P not stated); QoL: "improvement"; no data presented	—	—
Kim et al, 1999[51]	• Adverse effects of pleurodesis (doxycycline versus Helixor)	• Adverse effects: less pain, burning sensation, fever ($P < .05$)	—	—
Heiny et al, 1998,[68] Heiny and Albrecht, 1997[69]	• FACT V 3.0; ADR	• FACT V 3.0 ($P = .0001$); ADR: mucositis ($P = .03$)	• ADR: nausea, vomiting, diarrhea, hand-foot syndrome, chest pain (all favoring VAE)	—

(continued)

Table 4. (continued))

Author, Year	QoL Measure	Benefit From VAE, *P* Value, Specification of Improvement	No Benefit	Disadvantage
Heiny, 1991[48]	• QoL Index; Anxiety Scale	• QoL Index ($P \leq .01$); Anxiety Scale ($P \leq .01$)	—	—
RCTs on VAE concomitant with chemotherapy and radiotherapy				
Auerbach et al, 2005[47]	• EORTC QLQ-30; KPS; daily QoL report	—	• EORTC QLQ-C30; KPS; Daily QoL report	—
Lange et al (unpublished data, 1985)	• Nausea, vomiting, tumor pain; KPS	• Nausea ($P = .005$), vomiting ($P = .09$), tumor pain (trend); KPS ($P = .0008$ pre–post)	—	—
RCTs on VAE concomitant with radiotherapy				
Steuer-Vogt et al, 2001,[70] 2006[71]	• EORTC QLQ-C30	—	• EORTC QLQ-C30	—
Lenartz et al, 1996[72]	• Spitzer quality of life index	• Spitzer quality of life index (*P* not stated)	—	—
RCTs on perioperative VAE				
Enesel et al, 2005[73]	• KPS; Anxiety Scale	• KPS ($P < .01$ pre–post); Anxiety Scale ($P < .01$ pre–post)	—	—
Non-RCTs on VAE concomitant with chemotherapy alone or in combination with radiotherapy and hormones				
Loewe-Mesch et al, 2008[56]	• EORTC QLQ-C30, BR 23	• EORTC QLQ-C30: nausea/vomiting ($P = .02$); trend: constipation, sleep, dyspnea, pain, fatigue, social, cognitive, emotional functioning[c]; BR 23: systemic therapy side effects ($P = .02$); trend: sexual functioning and enjoyment[c]	• EORTC QLQ-C30, BR 23: remaining items[c]	• EORTC QLQ-C30; trend: diarrhea[c]
Beuth et al, 2008[60]	• Disease- or treatment-associated symptoms	• Odds ratio for occurrence of symptoms: 0.508 (95% CI = 0.319-0.811)[a], tumor pain, headache, fatigue, bleeding, mucositis[c]	• Sleep, cachexia[c]	• Gastrointestinal complaints, depression[c]
Matthes et al, 2007[59]	• ADR; disease- or treatment associated symptoms; KPS	• ADR ($P = .001$); Nausea/vomiting ($P < .001$), appetite ($P = .001$), back pain ($P = .02$), tiredness ($P = .001$), depression ($P < .0001$), irritability ($P = .005$), total symptom score ($P = .006$); KPS ($P < .001$)	• Diarrhea, tumor pain, memory, sleep	—
Friedel et al, 2007,[58] 2009[61]	• ADR; disease- or treatment-associated symptoms; KPS	• ADR ($P = .003$); Nausea/vomiting ($P = .007$), appetite ($P < .001$), diarrhea ($P = .004$), tiredness ($P = .009$), depression ($P < .001$), memory ($P = .04$), sleep ($P = .005$), irritability ($P = .031$), total symptom score ($P < .001$); KPS ($P < .001$ pre–post)	• Tumor pain, headache, mucositis	—
Bock et al, 2004[57]	• ADR[a]; disease-associated symptoms	• ADR ($P < .0001$); symptom-free 3.56 (95% CI = 2.03-6.29); vomiting, headache, exhaustion, depression, concentration, sleep, dizziness, irritability (all statistically significant); nausea (strong trend)	• Appetite, stomach pain, tumor pain, dyspnea, infections	—
Schumacher et al, 2003[62]	• Disease- or treatment-associated symptoms (score); KPS	• Symptom mean score ($P < .0001$); nausea ($P < .0001$), appetite ($P < .0001$), stomach pain $P < .0001$), tiredness ($P < .0001$), depression ($P < .0001$), concentration ($P < .0001$), irritability ($P < .0001$), sleep ($P = .0362$); KPS	• Headache, dyspnea	—

NOTE: VAE = Viscum album L extract; QoL = quality of life; RCT = randomized controlled trial; ADR = adverse drug reaction; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Cancer; BR = breast; STO = stomach; FACT = Functional Assessment of Cancer Therapy; FLIC = Functional Living Index–Cancer; GLQ = Global Life Quality; KPS = Karnofsky Performance Status Scale; TCM = Traditional Chinese Medicine Index; CI = confidence interval.

[a]Primary outcome.

[b]Improvements were seen for the "medium" dose not for the "low" or "high" doses (15, 5, or 35 ng mistletoe lectin/injection, respectively).

[c]Not adjusted for baseline imbalances.

Table 5. QoL Results of Studies on VAE Treatment Independent of Concomitant Conventional Cancer Treatments

Name, Year	QoL Measure	Benefit From VAE, *P* Value, Specification of Improvement	No Benefit	Disadvantage
RCT				
Grossarth and Ziegler, 2008[74]	Self-regulation questionnaire	Self-regulation ($P = .0012$)	—	—
Grossarth and Ziegler, 2007[53]	Self-regulation questionnaire	Self-regulation ($P = .014$)	—	—
Grossarth and Ziegler, 2007[75]	Self-regulation questionnaire	Self-regulation ($P = .0048$)	—	—
Grossarth and Ziegler, 2007[54]	Self-regulation questionnaire	Self-regulation ($P = .0002$)	—	—
Grossarth and Ziegler, 2006[55]	Self-regulation questionnaire	Self-regulation ($P = .034$)	—	—
Kleeberg, 2004,[63] Eggermont et al[76]	QoL evaluation	No data	No data	No data
Borrelli, 2001[46]	Spitzer Score (activity, daily living, health, support, outlook)	Spitzer Score ($P < .05$); well-being, daily life	—	—
Grossarth et al, 2001[77]	Self-regulation questionnaire	Self-regulation ($P = .022$)	—	—
Grossarth et al, 2001[77]	Self-regulation questionnaire	Self-regulation ($P = .13$)	—	—
Dold et al, 1991[49]	Subjective improvement of QoL, KPS, disease symptoms	Subjective improvement of QoL ($P = .04$)	KPS, disease symptoms	—
Non-RCT				
Grossarth and Ziegler, 2008[74]	Self-regulation questionnaire	Self-regulation ($P < .0005$)	—	—
Grossarth and Ziegler, 2007[53]	Self-regulation questionnaire	Self-regulation ($P < .0005$)	—	—
Grossarth and Ziegler, 2007[54]	Self-regulation questionnaire	Self-regulation ($P < .026$)	—	—
Grossarth and Ziegler, 2006[55]	Self-regulation questionnaire	Self-regulation ($P = .031$)	—	—

NOTE: VAE = *Viscum album* L extract; QoL = quality of life; RCT = randomized controlled trial.

Of the 4 nonblind trials using placebo or pseudoplacebo or active control treatment, all indicated a QoL benefit for VAE.

The methodologically best trials showing an improvement of QoL were the following:

- Two multicenter, double-blind, placebo-controlled RCTs (both by Semiglasov et al,[44,45] conducted in Russia, Bulgaria, and in the Ukraine) included 272 and 352 patients with breast cancer ($T_{1-3}N_{0-X}M_0$) receiving adjuvant chemotherapy (CMF—cyclophosphamide, methotrexate, fluorouracil). They found consistent and significant QoL advantages (in average scores) in the VAE patients (Table 4). One of these 2 RCTs investigated 3 dosages and found a benefit only for the medium dosage (containing 15 ng mistletoe lectin per injection); this dosage was then also applied in the second RCT).
- A multicenter RCT (by Piao et al[50] conducted in China) included 233 patients with lung, breast, or ovarian cancer ($T_{1-4}N_{0-3}M_{0-1}$) who were treated with VAE versus lentinan (antitumor polysaccharide isolated from shiitake mushroom), concomitant with chemotherapy. A significant advantage was observed (Table 4) in average QoL scores as well as in the proportion of patients who showed a QoL improvement.
- A large-scale epidemiological cohort study including 10 226 patients (by Grossarth et al[53-55,74,75,77] conducted in Germany) included 7 nested RCTs—on melanoma ($T_{3-4}N_0M_0$), cancer of the ovary (FIGO IA-IC), cervix uteri (FIGO IVA-IVB), corpus uteri (FIGO IA-IC), breast (in 2 RCTs: $T_{1-3}N_0M_0$ and IIIA-B), and several cancer types (all stages). In the framework of the cohort study, patients with these cancers had been matched pairwise for a broad range of disease-specific criteria, and 1 person in each pair was then randomly addressed for VAE treatment. The patients were then prospectively followed up in relation to psychosomatic self-regulation, survival, and tumor-specific outcomes. A benefit was found in all 7 RCTs (Table 5).
- An open-label RCT (conducted in Belgrade by Tröger et al[66,78]) included 95 breast cancer patients ($T_{1-3}N_{0-2}M_0$) receiving adjuvant chemotherapy (CAF: cyclophosphamide, doxorubicin, fluorouracil). A significant improvement of QoL in the VAE-treated group was found (Table 4).

Three trials could not find a benefit on QoL from VAE treatment:

- A small double-blind RCT (by Auerbach et al[47]) included 20 patients with breast cancer ($T_{1-2}N_0M_0$) receiving adjuvant chemotherapy (CMF) and radiotherapy (Table 4).
- A large, non-blind RCT (by Steuer-Vogt et al[70,71]), basically well-conducted though with an increasing dropout in relation to QoL assessment (32% after

1 year, 53% after 2 years), investigated patients with head and neck cancer (stage I-IV) after surgery and partly receiving radiotherapy. For additional VAE application, no statistically significant global benefit in QoL (EORTC QLQ-C30) could be found. In this study, QoL was primarily impaired in the subgroup of patients who received additional radiotherapy. Because QoL impairment is a precondition for a subsequent improvement and because other VAE studies found QoL improvement in patients receiving radiotherapy (Lange et al, unpublished data, 1985),[57,58,61,62,72] it would have been important to know whether any QoL changes occurred in this subgroup. However, this subgroup was not analyzed separately, although an initial stratification according to radiotherapy would have allowed such an analysis. Hence, this question remains open in this study.

- A small trial (by Büssing et al[67]) on 65 patients with breast cancer (stage not specified) receiving adjuvant chemotherapy (epirubicin and cyclophosphamide with or without fluorouracil) primarily investigated granulocyte function. It also mentions not finding a benefit for VAE application using the EORTC-QLQC30 and BR 23 questionnaire and the Rhodes Index, but it reported significantly less chemotherapy-related side effects in the VAE-treated group. This study was only published as an abstract and presented little information on study details and results. Despite randomized treatment allocation, study groups were not comparable at baseline, and a bias in cointervention seems to have occurred.

As regards details of the QoL assessment (see Tables 4 and 5), the most consistent improvement was reported in relation to self-regulation; a clear advantage for VAE-treated patients was reported in all studies. Frequent improvement was also reported in relation to fatigue, exhaustion, and sleep; nausea, vomiting, and appetite; and emotional well-being, sadness, anxiety, depression, irritability, or concentration difficulties. Repeatedly, though not as frequently as the former, the following areas improved: energy, functional well-being, ability to work, enjoyment of life, feeling ill, sexual interest, the thought of actually having treatment, and daily life. There was inconsistency in the results relating to pain, diarrhea or constipation, mucositis, and numbness. No improvement was observed in relation to loss of hair, dypnea, and infections. Often, the study reports did not present details when outcomes had not improved significantly and did not specify ADRs of conventional cancer drugs.

Safety

Tolerability was generally good: 1 case of urticaria and angioedema[50] and 1 case of "generalized reaction"[60] were described. Otherwise, no major side effects or toxicity were reported. Frequent, minor dose-dependent and spontaneously subsiding symptoms included reactions at the injection site (swelling, induration, erythema, pruritus, local pain) and mild flu-like symptoms or fever. In 1 study, local reactions were enhanced during concomitant chemotherapy.[56] After intrapleural instillation, VAE induced significantly fewer side effects than doxycycline.[51] Beyond these reviewed studies, a phase I study is currently being conducted at the NCCAM/NCI to investigate the safety and toxicity of and drug interactions between VAE and gemcitabine[6]; an interim analysis reports good tolerability, with neither dose-limiting toxicity of the VAE nor any effects on the plasma concentration of gemcitabine.[79]

Discussion

Most studies report a benefit regarding QoL in VAE-treated patients. This benefit mainly relates to psychosomatic self-regulation; to fatigue, sleep, exhaustion, and energy; to nausea, vomiting, and appetite; to emotional well-being, depression, anxiety, and concentration; to functional well-being and ability to work; and also, yet less consistently, to pain, diarrhea, general performance, and side effects of conventional cancer treatment. The benefit can be seen in VAE application concurrent with conventional cancer treatment (chemotherapy, radiation, and surgery)—where an improved tolerability of anticancer treatment is reported—and also independent of concomitant therapies. No dependence on type or stage of disease could be found. Most positive results were achieved in patients with breast cancer, whereas a study on head and neck cancer found no benefit for VAE. An increase in depression in VAE-treated patients was reported in 1 retrospective study investigating patient charts[60]; however, the results were not adjusted to apparent baseline imbalances such as significantly higher rates of hormone treatment in the VAE-treated patients, a side effect of which is depression; these results therefore require cautious interpretation.

In general, when appraising QoL effects, some principles have to be kept in mind. First, the particular QoL aspect has to be impaired in the beginning, otherwise any improvement of QoL is most unlikely to occur. This is for instance the case for performance status (KPS) in early-breast cancer patients receiving adjuvant CMF, as was the case in 3 of the reviewed VAE studies.[44,45,47] Second, timing is essential for QoL measurement. Widely spaced single-point estimates are less relevant and will differ from more continuous or repeated measurements (which are also clinically more relevant). Varying assessment periods might indeed explain some of the observed differences between patients' and physicians' symptom reports. Third, the QoL instrument has to have sufficient sensitivity for the condition or treatment in question. For instance, the sensitivity of the EORTC QLQ-C30 was called into question because it could not find a difference in 4 (out of 8 trials), whereas other questionnaires did find differences

in 2 of these 4 trials. Still, the EORTC QLQ-C30 did find a substantial difference in a recent well-conducted RCT[66,78] as well as in 2 other recently published small-sized RCTs.[52,65] A particular VAE-specific questionnaire[80] has been developed but was not applied in the reviewed studies.

Strengths and Weaknesses of the Review

The validity of this review largely depends on the primary trials. Although several of the more recent studies were reasonably well conducted, there were substantial weaknesses in others. Strengths and weaknesses of most of the reviewed trials have been described elsewhere (see references 29, 31, and 33) and are summarized in Table 2.

Still, specific methodological issues connected with QoL assessment remain to be considered. Some of the studies presented multiple comparisons without an a priori definition of the primary outcome and without statistical adjustment for multiple testing. Even though this practice is common also in most of the conventional cancer trials investigating QoL,[81] this makes it more difficult to differentiate positive results from pure chance effects. However, consistency of results across several outcomes or studies, as in the VAE trials, argues against mere chance.

Particularly in QoL studies, missing data are unavoidable but can induce bias when dropout is because of patients deteriorating or being discontented with treatment benefit. Accordingly, missing data bias cannot be excluded in some of the VAE studies. However, a number of the studies either had a small drop-out rate or the dropouts were unrelated to the outcome because they had occurred before baseline assessment. In these studies,[53-55,74] the patients were provisionally enrolled as matched pairs and subsequently asked for informed consent, and when they declined, they were excluded from the study together with their matched twin. The risk of bias is small with this procedure, but the conservative quality assessment in our review still assessed these studies as not having excluded a drop-out bias.

Questionnaires were mostly validated and well established. A post hoc validation[82] was conducted for the questionnaire on psychosomatic self-regulation used in several of the VAE studies: it assesses the ability to achieve well-being, inner equilibrium, appropriate stimulation, a feeling of competence, and a sense of being able to control stressful situations.

Placebo effects or participants giving the answer that they believe is wanted (obliging reporting) cannot be completely excluded even by rigorous blinding. Because blinded subcutaneous VAE injection can be identified correctly by doctors and patients,[47,83] blinding of VAE injections will hardly ever be reliable. Whether an insufficient pro forma blinding gives more valid results than an open application is, as yet, an unanswered question. Notwithstanding, 4 RCTs were double-blinded, and 3 of these had a positive result[44-46]; the 1 study finding no effect of VAE on QoL had a tiny sample size of 20 patients.[47] Five further trials compared VAE treatment with another control treatment (placebo,[48] pseudoplacebo,[49,50] or chemotherapy[51,52]). For instance, one of these studies was conducted in China where the applied control treatment lentinan is popular and well known and should also be able to induce competitive placebo effects.[50] All these 5 RCTs with control treatments found advantages for VAE. On the other hand, the only larger study finding no difference was not blinded.[71] In general, placebo application in cancer patients and best supportive care is associated only with limited improvement of symptoms such as pain and appetite and with hardly any improvement in QoL. Substantial, well-documented, patient-reported improvements in symptom control or QoL are unlikely to be a result of placebo effects.[84-86] Still, placebo effects and obliging reports cannot be completely ruled out in typical subcutaneous VAE application, but the available observations attest that the results are not merely illusory in nature.

Protection against performance (treatment) bias was rated low by us in most studies, although, in this regard, they do not differ substantially from common trial practice. The influence of cointerventions may quite generally be underestimated in clinical trials: When a control group improves less than the test group, control patients will have a greater urge to apply more additional relieving treatments, regardless of whether this is compliant with the care protocol. Notably, such cointerventions are not prevented by randomization, blinding, or care protocol. If they are documented, study groups can show substantial differences in cointervention frequencies that ultimately dilute the effect size of the test treatment (eg, Koes et al[87]). In one of the non-RCTs on VAE, the cointerventions were reported in detail, and indeed, the control group received significantly more additional interventions (glucocorticoids, enzymes, vitamins, trace elements).[56]

The inclusion of non-RCTs in this review might also raise the topic of bias because their internal validity—that is, unbiased comparability without randomized treatment allocation—is more difficult to generate. On the other hand, non-RCTs have the advantage of better external validity and can assess pros and cons of everyday practice without experimental artificialities (effectiveness). Four of the non-RCTs had a careful prospective matched-pair design, nested in a large cohort study (by Grossarth and Ziegler[53-55,74]): patients with ovarian, cervical, corpus uteri, or breast cancer (FIGO IA-IC, IB-IVA, IA-IC, or $T_{1-3}N_0M_0$, respectively) who reported on enrollment that they had already started VAE were closely matched to another cancer patient twin not using VAE and were then prospectively followed up (together with their twin).

Five retrolective non-RCTs (by Matthes et al,[59] Friedel et al,[58,61] Bock et al,[57] Schumacher et al,[62] and Beuth et al[60]) were multicenter, comparative, GEP (good epidemiological practice)-compliant, pharmacoepidemiological cohort studies[57-59,61,62] that investigated patient data from medical charts (selected according to predefined inclusion and exclusion criteria and without knowing the medical outcome) from a variety of medical centers on patients with pancreatic cancer (all stages),

colorectal cancer (stage I-III), or breast cancer (3 studies, stage I-III and all stages). Analysis was performed with multivariate adjustment for baseline differences or by computing a propensity score (in 1 study only the analysis of the primary outcome was adjusted). These studies were carefully and meticulously carried out according to a standardized procedure. Still, retrospective assessment of subjective outcomes without a primary standardization of the physician's charts leaves some uncertainty. Furthermore, only patients were included who received a single VAE preparation. This inclusion criterion might theoretically induce bias because patients with advancing disease may tend to switch VAE preparations.

To minimize publication bias in this review, a comprehensive search was conducted, and unpublished trials were also included. All but one of the identified unpublished studies could not be retrieved. We consider it unlikely that important trials with high methodological quality went unnoticed, at least in Europe. However, we cannot exclude the possibility that we missed minor ones or trials conducted in distant, non-European countries. Finally, in this review, the pragmatic definition of QoL led to the inclusion of more outcomes than just subjective well-being, insofar as ADRs also refer to somatic reactions. This, however, does not bias the review because all outcomes have been presented in connotation with the respective QoL instrument.

Clinical Relevance

In general, these studies indicate that VAEs might improve the subjective well-being of cancer patients. The explanation for such QoL improvement is only hypothetical at the current stage of knowledge. Endorphins enhanced by VAEs could be involved[88] as well as the immunological network,[89] which is also affected by VAEs. In the case of improved tolerability of anticancer treatments, the stabilization of DNA could also play a role.[6,18] Many other factors, including more psychological ones, also have to be considered.

Irrespective of any causal explanation, QoL is a clinically relevant topic. This is especially the case for cancer-related fatigue,[90,91] which is one of the most common unrelieved symptoms in the cancer context. It affects patients significantly and extensively, more than any other symptom such as anxiety, pain, nausea/vomiting, depression, alopecia, and so on.[91,92] It affects central aspects of their lives such as the ability to work, to take care of the family, to have relationships with friends, and to enjoy life.[92] Treatment options against cancer-related fatigue are limited to date; they are mainly behavioral, involving exercises and psychosocial interventions but also some medicines. Such treatments do show positive results in reducing fatigue but have small effect size and do not seem to offer adequate help to all patients.[93-95] By and large, the problem is still unsolved, and there is an urgent need to find further therapy options. Remarkably, most of the reviewed VAE studies described improvement in fatigue, exhaustion, and sleep in the course of treatment. This observation is also reported by individual patients and might explain the popularity of VAE in cancer.[96]

As far as nausea and vomiting caused by cancer treatment are concerned, a variety of highly effective interventions are available today, and VAE treatment could at best be seen in the perspective of an add-on.

A key issue for cancer patients is also their general functional and emotional well-being, including depression, anxiety, and concentration, which is also often reported to improve during VAE treatment. These aspects are interconnected with fatigue and are significant for patients. Because effective therapeutic approaches are presently limited, VAE treatment should be further investigated in this regard and its effects further analyzed.

Future Research

These studies indicate an improvement in QoL caused by VAE treatment. Future research should further investigate this effect and clear open questions regarding biological mechanisms, clinical significance, persistence of the improvement, dependence on dosage, disease stage, cancer site, and cointerventions. Because of the clinical relevance of cancer-related fatigue, VAE effects here should be further assessed using fatigue-specific questionnaires. Future VAE studies should take into account the general recommendation for clinical trials as well as the issues particularly connected with QoL assessment.[40,43,81]

Conclusions

VAE treatment seems to have an impact on QoL and reduces side effects of conventional therapies (chemotherapy, radiation) in experimental trials as well as in daily routine application. Fatigue, a debilitating symptom of cancer, seems to improve. The studies vary in the degree of methodological quality. Some of the weaknesses could be avoided by designing and conducting the studies carefully, whereas others represent typical and widely discussed problems of QoL research. Additional research should be conducted to further analyze the observations. Future studies should include questionnaires specifically designed to evaluate fatigue.

Acknowledgments

We thank the Gesellschaft für Biologische Krebsabwehr and the Software AG Stiftung for financially supporting this work.

Declaration of Conflicting Interests

Institute for Applied Epistemology and Medical Methodology has received restricted research grants from Weleda, Abnoba, and Helixor for other projects not connected to this review.

Funding

The Gesellschaft für Biologische Krebsabwehr and the Software AG Stiftung financially supported this work.

References

1. Molassiotis A, Fernandez-Ortega P, Pud D, et al. Use of complementary and alternative medicine in cancer patients: a European survey. *Ann Oncol.* 2005;16:655-663.
2. Fasching PA, Thiel F, Nicolaisen-Murmann K, et al. Association of complementary methods with quality of life and life satisfaction in patients with gynecologic and breast malignancies. *Support Care Cancer.* 2007;55:1277-1284.
3. Molassiotis A, Scott JA, Kearney N, et al. Complementary and alternative medicine use in breast cancer patients in Europe. *Support Care Cancer.* 2006;14:260-267.
4. Schwabe U, Paffrath D, eds. *Arzneiverordnungsreport 2005*. Heidelberg, Germany: Springer Verlag; 2005.
5. 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.
6. Mansky PJ, Grem J, Wallerstedt DB, Monahan BP, Blackman MR. Mistletoe and Gemcitabine in patients with advanced cancer: a model for the phase I study of botanicals and botanical-drug interactions in cancer therapy. *Integr Cancer Ther*. 2003;2:345-352.
7. Endo Y, Tsurugi K, Franz H. The site of action of the A-chain of mistletoe lectin I on eukaryotic ribosomes. *FEBS Lett.* 1988;231:378-380.
8. Stirpe F, Sandvig K, Olsnes S, Pihl A. Action of viscumin, a toxic lectin from mistletoe, on cells in culture. *J Biol Chem.* 1982; 257:13271-13277.
9. Stirpe F, Barbieri L, Battelli MG, Soria M, Lappi DA. Ribosome-inactivating proteins from plants: present status and future prospects. *Biotechnology (N Y).* 1992;10:405-412.
10. Peumans WJ, Verhaert P, Pfüller U, Van Damme EJM. Isolation and partial characterization of a small chitin-binding lectin from mistletoe (*Viscum album*). *FEBS Lett.* 1996;396: 261-265.
11. Klett CY, Anderer FA. Activation of natural killer cell cytotoxicity of human blood monocytes by a low molecular weight component from *Viscum album* extract. *Arzneimittelforschung*. 1989;39:1580-1585.
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. Orhan DD, Küpeli E, Yesilada E, Ergun F. Anti-inflammatory and antinociceptive activity of flavonoids isolated from *Viscum album* ssp. *album*. *Z Naturforsch C.* 2006;61:26-30.
14. Winkler K, Leneweit G, Schubert R. Characterization of membrane vesicles in plant extracts. *Colloids Surf B Biointerfaces*. 2005;45:57-65.
15. Jager S, Winkler K, Pfuller U, Scheffler A. Solubility studies of oleanolic acid and betulinic acid in aqueous solutions and plant extracts of *Viscum album* L. *Planta Med.* 2007;73: 157-162.
16. Kienle GS, Kiene H. *Die Mistel in der Onkologie: Fakten und konzeptionelle Grundlagen*. Stuttgart, Germany: Schattauer Verlag; 2003.
17. Büssing A, ed. *Mistletoe. The Genus* Viscum. Amsterdam, the Netherlands: Hardwood Academic; 2000.
18. Eggenschwiler J, von BL, Stritt B, et al. Mistletoe lectin is not the only cytotoxic component in fermented preparations of *Viscum album* from white fir (*Abies pectinata*). *BMC Complement Altern Med.* 2007;7:14.
19. Büssing A, Schietzel M. Apoptosis-inducing properties of *Viscum album* L. extracts from different host trees, correlate with their content of toxic mistletoe lectins. *Anticancer Res.* 1999;19:23-28.
20. Elsässer-Beile U, Lusebrink S, Grussenmeyer U, Wetterauer U, Schultze-Seemann W. Comparison of the effects of various clinically applied mistletoe preparations on peripheral blood leukocytes. *Arzneimittelforschung.* 1998;48:1185-1189.
21. Valentiner U, Pfüller U, Baum C, Schumacher U. The cytotoxic effect of mistletoe lectins I, II and III on sensitive and multidrug resistant human colon cancer cell lines in vitro. *Toxicology.* 2002;171:187-199.
22. Siegle I, Fritz P, McClellan M, Gutzeit S, Murdter TE. Combined cytotoxic action of *Viscum album* agglutinin-1 and anticancer agents against human A549 lung cancer cells. *Anticancer Res.* 2001;21:2687-2691.
23. Bantel H, Engels IH, Voelter W, Schulze-Osthoff K, Wesselborg S. Mistletoe lectin activates caspase-8/FLICE independently of death receptor signaling and enhances anticancer drug-induced apoptosis. *Cancer Res.* 1999;59:2083-2090.
24. Mueller EA, Anderer FA. Synergistic action of a plant rhamnogalacturonan enhancing antitumor cytotoxicity of human natural killer and lymphokine-activated killer cells: chemical specificity of target cell recognition. *Cancer Res.* 1990;50:3646-3651.
25. Zhu HG, Zollner TM, Klein-Franke A, Anderer FA. Enhancement of MHC-unrestricted cytotoxic activity of human CD56+CD3- natural killer (NK) cells and CD+T cells by rhamnogalacturonan: target cell specificity and activity against NK-insensitive targets. *J Cancer Res Clin Oncol.* 1994;(120): 383-388.
26. Park W-B, Lyu SY, Kim JH, et al. Inhibition of tumor growth and metastasis by Korean mistletoe lectin is associated with apoptosis and antiangiogenesis. *Cancer Biother Radiopharm.* 2001;16:439-447.
27. Van Huyen JP, Bayry J, Delignat S, et al. Induction of apoptosis of endothelial cells by *Viscum album*: a role for anti-tumoral properties of mistletoe lectins. *Mol Med.* 2002;8:600-606.
28. Kienle GS, Kiene H, Albonico HU. *Anthroposophic Medicine: Effectiveness, Utility, Costs, Safety*. Stuttgart, Germany: Schattauer Verlag; 2006.
29. Kienle GS, Kiene H. Complementary cancer therapy: a systematic review of prospective clinical trials on anthroposophic mistletoe extracts. *Eur J Med Res.* 2007;12:103-119.

30. Stauder H, Kreuser E-D. Mistletoe extracts standardised in terms of mistletoe lectins (ML I) in oncology: current state of clinical research. *Onkologie.* 2002;25:374-380.
31. 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. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2711058/. Accessed April 5, 2010.
32. National Cancer Institute. Mistletoe extracts (PDQ®). http://www.cancer.gov/cancertopics/pdq/cam/mistletoe/healthprofessional/allpages. Accessed April 5, 2010.
33. 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.
34. Ernst E, Schmidt K, Steuer-Vogt MK. Mistletoe for cancer? A systematic review of randomized clincial trials. *Int J Cancer.* 2003;107:262-267.
35. Horneber MA, Bueschel G, Huber R, Linde K, Rostock M. Mistletoe therapy in oncology. *Cochrane Database Syst Rev.* 2008;(2):CD003297.
36. Lange-Lindberg AM, Velasco Garrido M, Busse R. Misteltherapie als begleitende Behandlung zur Reduktion der Toxizität der Chemotherapie maligner Erkrankungen. GMS Health Technol Assess 2006. http://portal.dimdi.de/de/hta/hta_berichte/hta117_bericht_de.pdf. Accessed April 5, 2010.
37. Melzer J, Iten F, Hostanska K, Saller R. Efficacy and safety of mistletoe preparations (*Viscum album*) for patients with cancer diseases. *Forsch Komplementmed.* 2009;16:217-226.
38. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, ed. *Evaluation of Chemotherapeutic Agents*. New York, NY: Columbia University Press; 1949:191-205.
39. Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. Quality of life measurement: bibliographic study of patient assessed health outcome measures. *Br Med J.* 2002;324:1417.
40. Fayers PM, Machin D. *Quality of Life. The Assessment, Analysis and Interpretation of Patient-Reported Outcomes*. 2nd ed. Chichester, UK: Wiley; 2007.
41. Khan KS, ter Riet G, Glanville J, Sowden AJ, Kleijnen J. *Undertaking Systematic Reviews of Research on Effectiveness. CRD'S Guidance for those Carrying Out or Commissioning Reviews. CRD Report Number 4* (2nd ed.). York, UK: NHS Centre for Reviews and Dissemination; 2001.
42. Kleijnen J, Knipschild P. Mistletoe treatment for cancer: review of controlled trials in humans. *Phytomedicine.* 1994;1:255-260.
43. Efficace F, Bottomley A, Osoba D, et al. Beyond the development of health-related quality-of-life (HRQOL) measures: a checklist for evaluating HRQOL outcomes in cancer clinical trials—does HRQOL evaluation in prostate cancer research inform clinical decision making? *J Clin Oncol.* 2003;21:3502-3511.
44. 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.
45. 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.
46. Borrelli E. Evaluation of the quality of life in breast cancer patients undergoing lectin standardized mistletoe therapy. *Minerva Med.* 2001;92(suppl 1):105-107.
47. 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, Fintelmann V, Kemper FH, Schilcher H, eds. *Fortschritte in der Misteltherapie. Aktueller Stand der Forschung und klinischen Anwendung*. Essen, Germany: KVC Verlag; 2005:543-554.
48. Heiny B-M. Additive Therapie mit standardisiertem Mistelextrakt reduziert die Leukopenie und verbessert die Lebensqualität von Patientinnen mit fortgeschrittenem Mammakarzinom unter palliativer Chemotherapie (VEC-Schema). *Krebsmedizin.* 1991;12:1-14.
49. Dold U, Edler L, Mäurer HCh, et al. *Krebszusatztherapie beim fortgeschrittenen nicht-kleinzelligen Bronchialkarzinom.* Stuttgart, Germany: Georg Thieme Verlag; 1991.
50. 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.* 2004;24:303-309.
51. Kim M-H, Park Y-K, Lee S-H, 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 J Med.* 1999;57(suppl II):S121.
52. Longhi A, Mariani E, Kuehn JJ. A randomized study with adjuvant mistletoe versus oral Etoposide on post relapse disease-free survival in osteosarcoma patients. *Eur J Integr Med.* 2009;1:27-33.
53. Grossarth-Maticek R, Ziegler R. Prospective controlled cohort studies on long-term therapy of cervical cancer patients with a mistletoe preparation (Iscador®). *Forsch Komplementmed.* 2007;14:140-147.
54. Grossarth-Maticek R, Ziegler R. Prospective controlled cohort studies on long-term therapy of ovarian cancer patients with mistletoe (*Viscum album* L.) extracts Iscador. *Arzneimittelforschung.* 2007;57:665-678.
55. Grossarth-Maticek R, Ziegler R. Prospective controlled cohort studies on long-term therapy of breast cancer patients with a mistletoe preparation (Iscador). *Forsch Komplementmed.* 2006;13:285-292.

56. Loewe-Mesch A, Kuehn JH, Borho K, et al. Adjuvante simultane Mistel-/Chemotherapie bei Mammakarzinom: Einfluss auf Immunparameter, Lebensqualität und Verträglichkeit. *Forsch Komplementmed.* 2008;15:22-30.
57. Bock PR, Friedel WE, Hanisch J, Karasmann M, Schneider B. Wirksamkeit und Sicherheit der komplementären Langzeitbehandlung mit einem standardisierten Extrakt aus Europäischer Mistel (*Viscum album* L.) zusätzlich zur konventionellen adjuvanten onkologischen Therapie bei primärem, nicht metastasiertem Mammakarzinom. Ergebnisse einer multizentrischen, komparativen, epidemiologischen Kohortenstudie in Deutschland und der Schweiz. *Arzneimittelforschung.* 2004;54:456-466.
58. Friedel WE, Matthes H, Bock PR. Mistletoe in supportive care in patients with primary non-metastatic colorectal carcinoma. Paper presented at the ASMO Conference Lugano; 5-8 July, 2007; Lugano, Switzerland.
59. Matthes H, Friedel WE, Bock PR. Supportive care in pancreatic carcinoma patients treated with a fermented mistletoe (*Viscum album* L.) extract. Paper presented at the ASMO Conference Lugano; 5-8 July, 2007; Lugano, Switzerland.
60. 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.* 2008;28:523-528.
61. Friedel WE, Matthes H, Bock PR, Zänker KS. 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.* 2009;7:137-145.
62. Schumacher K, Schneider B, Reich G, et al. Influence of postoperative complementary treatment with lectin-standardized mistletoe extract on breast cancer patients: a controlled epidemiological multicentric retrolective cohort study. *Anticancer Res.* 2003;23:5081-5088.
63. Kleeberg UR, Suciu S, Bröcker EB, et al. Final results of the EORTC 18871/DKG 80-1 randomised phase III trial: rIFN-α2b versus rIFN-γ versus Iscador M versus observation after surgery in melanoma patients with either high-risk primary (thickness >3mm) or regional lymph node metastasis. *Eur J Cancer.* 2004;40:390-402.
64. Cazacu M, Oniu T, Lungoci C, et al. The influence of Isorel on the advanced colorectal cancer. *Cancer Biother Radiopharm.* 2003;18:27-34.
65. Eisenbraun J. Verbesserung der Lebensqualität durch eine Misteltherapie (abnobaVISCUM©) bei Patienten mit Magenkarzinom: Ergebnisse einer randomisierten, kontrollierten Studie. *Zeitschrift für Phytotherapie* 30 (S 01):DOI: 10.1055/s-0029-1239850, 2009.
66. Tröger W, Matijaševic M, Ždrale Z, Tisma N, Jezdic S. Additional therapy with mistletoe extracts in breast cancer patients receiving chemotherapy: a prospective randomized open label pilot study. In: Scheer R, Alban S, Becker H, et al, eds. *Die Mistel in der Tumortherapie 2. Aktueller Stand der Forschung und klinische Anwendung*. Essen, Germany: KVC-Verlag; 2009. p. 509-21.
67. Büssing A, Brückner U, Enser-Weis U, et al. Modulation of chemotherapy-associated immunosuppression by intravenous application of *Viscum album* L. extract (Iscador): a randomised physe II study. *Eur J Integr Med.* 2008;1(suppl 1):S44-S54.
68. Heiny B-M, Albrecht V, Beuth J. Lebensqualitätsstabilisierung durch Mistellektin-1 normierten Extrakt beim fortgeschrittenen kolorektalen Karzinom. *Onkologe.* 1998;4(suppl 1):35-39.
69. Heiny B-M, Albrecht V. Komplementäre Therapie mit Mistellektin-1-normiertem Extrakt. Lebensqualitätsstabilisierung beim fortgeschrittenen kolorektalen Karzinom: Fakt oder Fiktion? *Med Welt.* 1997;48:419-423.
70. 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.* 2001;37:23-31.
71. Steuer-Vogt MK, Bonkowsky V, Scholz M, Fauser C, Licht K, Ambrosch P. Einfluss eines ML-1-normierten Mistelextraktes auf die Lebensqualität bei Patienten mit Kopf-Hals-Karzinomen. *HNO.* 2006;54:277-286.
72. 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.
73. Enesel MB, Acalovschi I, Grosu V, et al. Perioperative application of the *Viscum album* extract Isorel in digestive tract cancer patients. *Anticancer Res.* 2005;25:4583-4590.
74. Grossarth-Maticek R, Ziegler R. Randomized and nonrandomized 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.
75. Grossarth-Maticek R, Ziegler R. Wirksamkeit und Unbedenklichkeit einer Langzeitbehandlung von Melanompatienten mit einem Mistelpräparat (Iscador®). *Schweiz Z Ganzheitsmed.* 2007;19:325-332.
76. Eggermont A, Kleeberg UR, Ruiter DJ, Suciu 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, ed. *American Society of Clinical Oncology Educational Book*. Baltimore, MD: Lippincott Williams & Wilkins; 2001:88-93.
77. 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. *Altern Ther Health Med.* 2001;7:57-78.
78. Tröger W, Jezdic S, Zdrale 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.* 2009;3:35-45.
79. Mansky PJ, Wallerstedt DB, Monahan BP, et al. Phase I study of mistletoe extract/gemcitabine combination treatment in patients with advanced solid tumors. *Onkologie.* 2008;31(suppl 1):200.
80. Kirchberger I, Wetzel D, Finger T. Development and validation of an instrument to measure the effects of a mistletoe preparation on quality of life of cancer patients: the Life Quality Lectin-53 (LQL-53) Questionnaire. *Qual Life Res.* 2004;13:463-479.
81. Joly F, Vardy J, Pintilie M, Tannock IF. Quality of life and/or symptom control in randomized clinical trials for patients with advanced cancer. *Ann Oncol.* 2007;18:1935-1942.
82. Büssing A, Girke M, Heckmann C, Schad F, Ostermann T, Kröz M. Validation of the self-regulation questionnaire as a measure of health in quality of life research. *Eur J Med Res.* 2009;14:223-227.
83. Rostock M, Huber R. Randomized and double-blind studies: demands and reality as demonstrated by two examples of mistletoe research. *Forsch Komplementmed.* 2004;11(suppl 1): 18-22.
84. Chvetzoff G, Tannock I. Placebo effects in oncology. *J Natl Cancer Inst.* 2003;95:19-29.
85. Hróbjartsson A, Gøtzsche P. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med.* 2001;344:1594-1602.
86. Kienle GS, Kiene H. The powerful placebo effect: fact or fiction? *J Clin Epidemiol.* 1997;50:1311-1318.
87. Koes BW, Bouter LM, van Mameren H, et al. Randomised clinical trial of manipulative therapy and physiotherapy for resistant back and neck complaints: results of one year follow up. *Br Med J.* 1992;304:601-605.
88. Heiny B-M, Beuth J. Mistletoe extract standardized for galactoside-spcific lectin (ML-1) induces β-endorphin release and immunopotentiation in breast cancer patients. *Anticancer Res.* 1994;14:1339-1342.
89. Büssing A, Tröger W, Stumpf C, Schietzel M. Local reactions to treatments with *Viscum album* L. extracts and their association with T-lymphocyte subsets and quality of life. *Anticancer Res.* 2008;28:1893-1898.
90. Curt G, Johnston PG. Cancer fatigue: the way forward. *Oncologist.* 2003;8(suppl 1):27-30.
91. Stone P, Richardson A, Ream E, Smith AG, Kerr DJ, Kearney N. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. Cancer Fatigue Forum. *Ann Oncol.* 2000;11:971-975.
92. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: the scale of the problem. *Oncologist.* 2007;12(suppl 1):4-10.
93. Ahlberg K, Ekmann T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. *Lancet.* 2003;362:640-650.
94. Carroll JK, Kohli S, Mustian KM, Roscoe JA, Morrow GR. Pharmacologic treatment of cancer-related fatigue. *Oncologist.* 2007;12(suppl 1):43-51.
95. Mustian KM, Morrow GR, Carroll JK, Figueroa-Moseley CD, Jean-Pierre P, Williams GC. Integrative nonpharmacologic behavioral interventions for the management of cancer-related fatigue. *Oncologist.* 2007;12(suppl 1):51-67.
96. Wode K, Schneider T, Lundberg I, Kienle GS. Mistletoe treatment in cancer-related fatigue: a case report. *Cases J.* 2009;2:77.