



# Mistletoe in oncological treatment: a systematic review

## Part 1: survival and safety

M. Freuding<sup>1</sup> · C. Keinki<sup>1</sup> · O. Micke<sup>2</sup> · J. Buentzel<sup>3</sup> · Jutta Huebner<sup>1</sup>

Received: 26 November 2018 / Accepted: 31 December 2018 / Published online: 23 January 2019  
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

### Abstract

**Purpose** Mistletoe treatment of cancer patients is discussed highly controversial in the scientific literature. Aim of this systematic review is to give an extensive overview about current state of research concerning mistletoe therapy of oncologic patients regarding survival, quality of life and safety.

**Methods** In September and October 2017 Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, CINAHL and “Science Citation Index Expanded” (Web of Science) were systematically searched.

**Results** The search strategy identified 3647 hits and 28 publications with 2639 patients were finally included in this review. Mistletoe was used in bladder cancer, breast cancer, other gynecological cancers (cervical cancer, corpus uteri cancer, and ovarian cancer), colorectal cancer, other gastrointestinal cancer (gastric cancer and pancreatic cancer), glioma, head and neck cancer, lung cancer, melanoma and osteosarcoma. In nearly all studies, mistletoe was added to a conventional therapy. Patient relevant endpoints were overall survival (14 studies,  $n = 1054$ ), progression- or disease-free survival or tumor response (10 studies,  $n = 1091$ ). Most studies did not show any effect of mistletoe on survival. Especially high quality studies do not show any benefit.

**Conclusions** With respect to survival, a thorough review of the literature does not provide any indication to prescribe mistletoe to patients with cancer.

**Keywords** Mistletoe · Cancer · Complementary and alternative medicine (CAM) · Patient-relevant outcomes

---

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s00432-018-02837-4>) contains supplementary material, which is available to authorized users.

---

✉ Jutta Huebner  
jutta.huebner@med.uni-jena.de

<sup>1</sup> Klinik für Innere Medizin II, Hämatologie und Internistische Onkologie, Universitätsklinikum Jena, Am Klinikum 1, 07747 Jena, Germany

<sup>2</sup> Klinik für Strahlentherapie und Radioonkologie, Franziskus Hospital, Kiskerstraße 26, 33615 Bielefeld, Germany

<sup>3</sup> Klinik für Hals-Nasen-Ohren-Heilkunde, Südharzlinikum Nordhausen, Dr.-Robert-Koch-Straße 39, 99734 Nordhausen, Germany

## Background

Mistletoe (*Viscum album*) is a small plant which grows as hemiparasites on a wide range of host trees in Europe, Asia and North Africa. Contents of mistletoes are vincetoxins, lectins, polysaccharides, flavonoids, triterpenes and polypeptides (Huebner 2008).

There are two different groups of mistletoe supplements. On the one hand phytotherapeutic mistletoe extracts are standardized on a certain lectin level (e.g. Cefalektin®, Eurixor®, Lektinol®) and on the other hand there are anthroposophical or homeopathically produced mistletoe supplements (e.g. Abnoba viscum®, Helixor®, Iscador®, Iscucin®, Isorel®) (Lange-Lindberg et al. 2006). Two different kinds of positive mechanisms of mistletoe are discussed in literature. First, some authors support the thesis that mistletoe has a direct or indirect anti-tumoral effect either via cytotoxic substances or via lectins which activate the immune system. Second, according to some authors mistletoe shall improve

well-being and quality of life and reduce side effects, maybe by endorphin release.

Mistletoe treatment of cancer patients is discussed highly controversial in the scientific literature. On the one hand, some authors suggested a clear benefit of mistletoe treatment regarding quality of life (Melzer et al. 2009; Kienle and Kiene 2007, 2010; Kienle et al. 2009; Bussing et al. 2012), survival (Ostermann, 2009), toxicity of main intervention (Kienle and Kiene 2007, 2010; Kienle et al. 2009) and possible also tumor remission and survival (Kienle and Kiene 2007; Kienle et al. 2009). On the other hand, Ernst et al. (2003) concluded that mistletoe treatment has no benefit for cancer patients. Further Horneber et al. (2008) and Lange-Lindberg et al. (2006) concluded that results regarding efficacy concerning survival and toxicity reduction were insufficient. However, their results also provide first support that mistletoe seems to improve quality of life in general (Horneber et al. 2008) or at least for breast cancer patients in Germany (Lange-Lindberg et al. 2006). All authors of these systematic reviews and meta-analysis were relatively conform about the great heterogeneity and the more or less insufficient methodological quality of clinical mistletoe research to that date. As even the newest one of these works was published several years ago, a systematic summary also including recent literature regarding mistletoe is lacking.

## Objectives

Aim of this systematic review is to give an extensive overview about current state of research concerning mistletoe therapy of oncologic patients. Important outcomes considered in this context were efficacy of mistletoe treatment regarding survival, quality of life and safety.

Results are presented in two publications. Part 1 (this publication) presents all data of the systematic search and on survival data as well as on safety under mistletoe therapy. Part 2 (submitted to *J Cancer Res Clin Oncol*) presents all data on quality of life and on impact on toxicity of cancer treatment under mistletoe therapy.

## Methods

### Criteria for including studies in this review

Regarding study type, only randomized controlled studies were included in this review. All other inclusion and exclusion criteria are listed in Table 1 based on a PICO-Schema.

### Search strategy

In September and October 2017, the following databases were systematically searched: Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, CINAHL and “Science Citation Index Expanded” (Web of Science). For every database a complex search strategy was developed consisting of a combination of Mesh-Terms/keywords and text words regarding cancer and mistletoe. The search string was not restricted by filter of study type to make sure that no randomized controlled trial would be missed. Only articles published in English or German and published after 1994 were considered. The exact search strategy for each database is listed in Table 2.

**Table 1** Inclusion and exclusion criteria

PICO	Inclusion criteria	Exclusion criteria
Patient	Cancer Patients (all entities and stages) Adult patients (age > 18)	Patients with precancerous conditions or Carcinoma in situ Primary prevention Preclinical studies
Intervention	Every intervention with mistletoe extract No restrictions regarding mistletoe extract, dose, mode of application	
Comparison	All possible control groups (active control, placebo, standard/guideline/usual Care, wait list)	
Outcome	Mortality (overall survival) Morbidity (progression/disease free interval, Tumor response) Patient Reported Outcomes (i.e. Quality of Life or other important psychological outcomes) Toxicity and adverse events (CTCAE)	Only laboratory parameters
Others	Language: German and English Full publication Studies published since 1995	Grey literature (conference articles, abstracts, letters, ongoing studies, unpublished literature...)

**Table 2** Search strategies for each database

Database	Search strategy (2017/26/09–2017/10/11)
Medline/Embase via Ovid	1. mistletoe\$.mp. or exp Mistletoe/ or viscum album.mp. or exp Viscum album/ or (“ABNOBAViscum” or “Lektinol” or “Plenosol” or “Isorel” or “Iscucin” or “Iscador” or “Iscar” or “Helixor” or “Eurixor” or “Vysorel”).mp 2. exp neoplasms/ or neoplasm\$.mp. or cancer\$.mp. or tumo?r\$.mp. or malignan\$.mp. or oncolog\$.mp. or carcinom\$.mp. or leuk?emia.mp. or lymphoma.mp. or sarcom\$.mp 3. 1 and 2 4. limit 3 to english or limit 3 to german
CENTRAL	#1. [mh mistletoe] or mistletoe? or “Viscum album” or “Viscum” or “ABNOBAViscum” or “Lektinol” or “Plenosol” or “Isorel” or “Iscucin” or “Iscador” or “Iscar” or “Helixor” or “Eurixor” or “Vysorel” #2. [mh neoplasms] or neoplasm* or cancer? or tumo#r? or malignan* or oncolog* or carcinom* or leuk*mia or “lymphoma” or sarcoma? #3. #1 and #2
CINAHL	S1. (MH “Mistletoe” OR TX Mistletoe OR TX “Viscum album” OR TX “Viscum” OR TX “ABNOBAViscum” OR TX “Lektinol” OR TX “Plenosol” OR TX “Isorel” OR TX “Iscucin” OR TX “Iscador” OR TX “Iscar” OR TX “Helixor” OR TX “Eurixor” OR TX “Vysorel”) S2. MH “Neoplasms+” OR TX neoplasm* OR TX cancer OR TX tumo#r OR TX malignan* OR TX oncolog* OR TX carcinom* OR TX leuk#emia OR TX lymphoma OR TX sarcoma S3. (LA German OR LA English) S4. S1 AND S2 AND S3
PsycINFO	S1. (TX Mistletoe OR TX “Viscum album” OR TX “Viscum” OR TX “ABNOBAViscum” OR TX “Lektinol” OR TX “Plenosol” OR TX “Isorel” OR TX “Iscucin” OR TX “Iscador” OR TX “Iscar” OR TX “Helixor” OR TX “Eurixor” OR TX “Vysorel”) S2. ((DE “Neoplasms” OR DE “Benign Neoplasms” OR DE “Breast Neoplasms” OR DE “Endocrine Neoplasms” OR DE “Leukemias” OR DE “Melanoma” OR DE “Metastasis” OR DE “Nervous System Neoplasms” OR DE “Terminal Cancer”) OR (TX neoplasm* OR TX cancer OR TX tumo#r OR TX malignan* OR DE “oncology” OR TX oncolog* OR TX carcinom* OR TX leuk#emia OR TX lymphoma OR TX sarcoma) S3. (LA German OR LA English) S4. S1 AND S2 AND S3
Science Citation Index Expanded (Web of Science)	#1. (TS = Mistletoe* OR TS = “Viscum album” OR TS = Viscum OR TS = “ABNOBAViscum” OR TS = “Lektinol” OR TS = “Plenosol” OR TS = “Isorel” OR TS = “Iscucin” OR TS = “Iscador” OR TS = “Iscar” OR TS = “Helixor” OR TS = “Eurixor” OR TS = “Vysorel”) #2. (TS = neoplasm* OR TS = cancer OR TS = cancers OR TS = > tumo\$r OR TS = tumo\$rs OR TS = malignan* OR TS = oncolog* OR TS = carcinom* OR TS = leuk\$emia OR TS = lymphoma OR TS = sarcoma OR TS = sarcomas) #3. #1 AND #2

## Data collection and analysis

### Selection of studies

Study selection of this review was made in three steps. First, titles and abstracts of all studies were screened by two independent reviewers (MF, JH) regarding their relevance for this review. Reasons for rejecting studies at this stadium were irrelevant topics, other study types than randomized controlled studies and preclinical studies. Second, full texts from all remaining studies were screened and again it was decided if they matched with inclusion criteria. In the last step, studies were excluded if they were double publications or reported no patient relevant outcome. These excluded studies are listed in the section “[Excluded studies](#)”.

### Data extraction and management

Data extraction was made by MF and JH independently as well as evaluation of study quality. In case of disagreement, consensus was made by discussion.

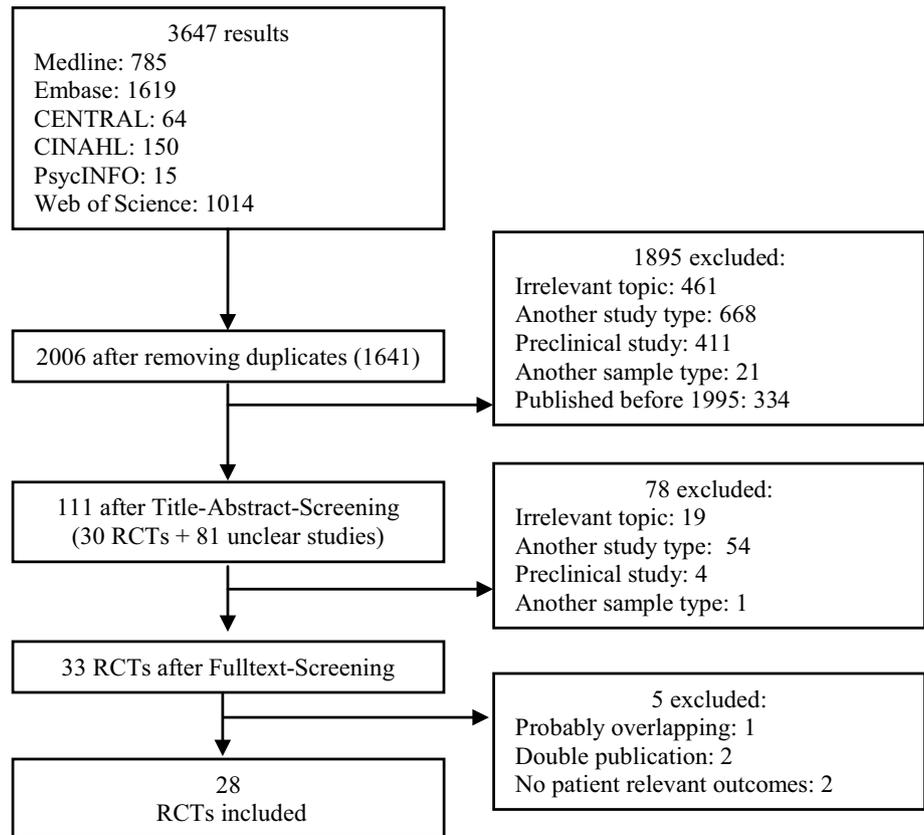
### Assessment of risk of bias in included studies

The risk of bias in the included studies was judged by MF and CK independently based on Cochrane risk of Bias tool (Higgins et al. 2017). Apart from that, methodological quality of the studies was also analyzed with SIGN checklists and was narratively described by the authors. Relevant aspects from this analysis were noted. In case of disagreement, consensus was again made by discussion.

## Results

The search revealed 3647 hits. After removing duplicates, 2006 studies remained. From these 111 articles were selected to complete review and 33 RCTs of these studies were considered as relevant. Finally, 28 publications were included in this review (see Fig. 1). In some of these publications, data from one study were described (first study and follow-up (Troger et al. 2013, 2014a), different outcomes reported per publication (Lenartz et al. 1996, 2000;

Fig. 1 Consort diagram



Steuer-Vogt et al. 2001, 2006). In one case, four publications described one set of patients from a study with three arms. Two publications reported the results of one treatment arm, respectively, versus the control group (Troger et al. 2009, 2014b) and the remaining two publications were follow-up studies of the former (Troger et al. 2012, 2016). Moreover, there were two publications reporting two different datasets of patients (with and without metastasis) in one article (Grossarth-Maticek and Ziegler 2007b, 2008). Accordingly, the included 28 publications reported data from 24 different studies.

### Characteristics of included studies

Altogether, 2639 patients (mean per study = 109.96, SD = 119.73; 60% female, 37% male; missing value  $n = 1$ ) were analyzed with median range of age from 50 to 65 years (reported in 7 studies) or on average a mean age of 48.80 years (SD = 7.28, reported in 8 studies). In nine studies, no information on age was given. Eleven studies were carried out in Germany (46%), two studies in Serbia and two in Egypt (8% each), one (4%) in China, Israel, Italy, Korea each and finally three studies in several countries (12%). Two of these included patients from Bulgaria, Russia and Ukraine and one study patients from Germany, France, Switzerland, Austria, Belgium, Great, Britain,

Yugoslavia, Israel, Czechia, Estonia, Spain, Greece, Poland. In two studies (8%) no country was reported.

The following cancer types (reported with number of included patients and percentage of whole population of this review) were included in the studies (a detailed presentation can be found as table S1 as a supplementary material):

- Bladder cancer (Goebell et al. 2002): one study,  $n = 44$  (2%)
- Breast cancer (Grossarth-Maticek and Ziegler 2006a, b; Semiglasov et al. 2004; Semiglasov et al. 2006; Troger et al. 2009, 2012, 2014b, 2016): five studies,  $n = 824$  (31%)
- Colorectal cancer (Cazacu et al. 2003; Heiny and Albrecht 1997): two studies,  $n = 143$  (5%)
- Other gastrointestinal cancer [gastric cancer (Kim et al. 2012), pancreatic cancer (Tröger et al. 2013, 2014)]: two studies,  $n = 249$  (9%)
- Glioma (Lenartz et al. 1996, 2000): one study,  $n = 29$  (1%)
- Other gynecological cancers [cervical cancer (Grossarth-Maticek and Ziegler 2007b), corpus uteri cancer (Grossarth-Maticek and Ziegler 2008), ovarian cancer (Grossarth-Maticek and Ziegler 2007c)]: five studies,  $n = 232$  (9%)

- Head and neck cancer: (Steuer-Vogt et al. 2001, 2006): one study,  $n = 477$  (18%)
- Lung cancer (Bar-Sela et al. 2013): one study,  $n = 72$  (3%)
- Melanoma (Grossarth-Maticek and Ziegler 2007a; Kleeberg et al. 2004): two studies,  $n = 248$  (9%)
- Osteosarcoma (Longhi et al. 2014): one study  $n = 20$  (1%)
- Various cancers (El-Kolaly et al. 2016; Gaafar et al. 2014; Piao et al. 2004): three studies,  $n = 301$  (11%)

The studies used various forms of mistletoe interventions (see Table S1). In 12, i.e. half of the included studies ( $n = 902$ ), patients received Iscador® (Bar-Sela et al. 2013; Grossarth-Maticek and Ziegler 2006a, b, 2007b, c, 2008; Kleeberg et al. 2004; Longhi et al. 2014; Piao et al. 2004; Troger et al. 2013, 2014a). In two studies (8%) they received Eurixor® ( $n = 506$ ) (Steuer-Vogt et al. 2001, 2006), Viscum-Fraxini® ( $n = 68$ ) (El-Kolaly et al. 2016; Gaafar et al. 2014) or Lektinol® ( $n = 624$ ) (Semiglasov et al. 2004; Semiglasov et al. 2006). In one study each (4%) AbnobaViscum® ( $n = 29$ ) (Kim et al. 2012) and Isorel® ( $n = 64$ ) (Cazacu et al. 2003) was investigated. Furthermore, in one study the control group was compared to Iscador® on the one hand (Troger et al. 2009, 2012) and to Helixor® on the other hand (Troger et al. 2014b, 2016) ( $n = 90$ ). Finally, in two studies the authors only reported that patients receive mistletoe lectin ( $n = 123$ ) (Goebell et al. 2002; Heiny and Albrecht 1997).

In nearly all studies, mistletoe was added to another (conventional) therapy. In one study, patients only received best supportive care (Troger et al. 2013, 2014a). Conventional therapies in the remaining studies were:

- Mistletoe treatment simultaneously to chemotherapy: four studies,  $n = 657$  (Bar-Sela et al. 2013; Piao et al. 2004; Semiglasov et al. 2004; Semiglasov et al. 2006).
- Mistletoe treatment after surgery: three studies,  $n = 268$  (Goebell et al. 2002; Kleeberg et al. 2004; Longhi et al. 2014).
- Mistletoe treatment after surgery and simultaneously to chemotherapy: four studies,  $n = 482$  (Cazacu et al. 2003; Heiny and Albrecht 1997; Kim et al. 2012; Troger et al. 2009, 2012, 2014b, 2016).
- Mistletoe treatment after surgery and radiotherapy: one study,  $n = 29$  (Lenartz et al. 1996, 2000).
- In one arm mistletoe treatment after surgery and in another one after surgery and radiotherapy: one study,  $n = 477$  (Steuer-Vogt et al. 2001, 2006).
- Mistletoe treatment as pleurodesis: two studies,  $n = 68$  (El-Kolaly et al. 2016; Gaafar et al. 2014).
- Mistletoe treatment in combination with not further described conventional therapy:  $n = 342$ , eight studies (Grossarth-Maticek and Ziegler 2006a, b, 2007a, b, c, 2008)

In most studies the control group received no additional intervention to the same conventional therapy as mistletoe group (20 studies, 83%). Semiglasov et al. (2004) and Semiglasov et al. (2006) reported only studies in which the control group received a placebo medication. In one study with three arms, mistletoe treatment was compared to one control group receiving the same conventional therapy as treatment arm and to one group treated with no conventional postoperative treatment (Cazacu et al. 2003). Finally, in one small study the control group was treated with Etoposide compared to mistletoe in the treatment group (Longhi et al. 2014) and in another study mistletoe treatment was compared to the phytopharmakon Lentinan, a polysaccharide is derived from the mycelium of the Shitake mushroom body (Piao et al. 2004).

The following main patient relevant endpoints were reported (see table S1): overall survival (OS, 14 studies,  $n = 1054$ ), morbidity (progression- or disease-free survival PFS/DFS, tumor response, ten studies,  $n = 1091$ ), quality of life (QoL, 17 studies,  $n = 2167$ ) and toxicity of main intervention (11 studies,  $n = 1409$ ). Apart from that, two studies with 68 various cancer patients in sum examined the efficacy of mistletoe as palliative treatment for malignant pleural effusion (El-Kolaly et al. 2016; Gaafar et al. 2014).

### Excluded studies

Both randomized datasets analyzed in Grossarth-Maticek et al. (2001) were excluded. One dataset was based on breast cancer patients. This dataset was re-analyzed in Grossarth-Maticek and Ziegler (2006b) which is included in this systematic review. The second dataset based on various cancer types was excluded because it is not clear if this dataset is overlapping with the later one in Grossarth-Maticek and Ziegler (2007b); Grossarth-Maticek and Ziegler (2007c); Grossarth-Maticek and Ziegler (2008). Apart from that two double publications were excluded. Schierholz et al. (2003) is a German publication of Piao et al. (2004) and Troger (2011) is the same article in German as Troger et al. (2009). Finally, Heiny et al. (1998) and Schink et al. (2007) were not considered because they did not examine patient relevant outcomes.

### Risk of bias in included studies

In Table 3 risk of bias based on the judgment of methodological quality considered by the Cochrane Risk of Bias Tool (Higgins et al. 2017) is presented.

First, selection bias describes the risk of systematic differences between baseline characteristics of treatment and control group. In 13 studies a small risk (Table 3 characterized as +: low risk) was judged, in 7 studies a high risk is likely, whereas in the remaining 6 studies there was an

**Table 3** Risk of Bias in included studies

Study	RSQ	AC	BPP	BOA	IOD	SR	OSB
Bar-Sela et al. (2013)	+	+	-	-	-	+	-
Cazacu et al. (2003)	?	?	-	-	-	-	-
El-Kolaly et al. (2016)	-	-	-	-	+	+	-
Gaafar et al. (2014)	?	?	-	-	+	+	-
Goebell et al. (2002)	+	+	-	-	+	+	-
Grossarth-Maticek and Ziegler (2006b)	-	-	-	-	+	-	-
Grossarth-Maticek and Ziegler (2006a)	-	-	-	-	-	-	-
Grossarth-Maticek and Ziegler (2007b)	-	-	-	-	-	-	-
Grossarth-Maticek and Ziegler (2007c)	-	-	-	-	-	-	-
Grossarth-Maticek and Ziegler (2007a)	-	-	-	-	+	+	-
Grossarth-Maticek and Ziegler (2008)	-	-	-	-	-	-	-
Heiny and Albrecht (1997)	+	?	-	-	-	-	-
Kim et al. (2012)	+	+	-	-	-	-	-
Kleeberg et al. (2004)	+	+	-	-	+	+	+
Lenartz et al. (2000)	?	?	-	+	-	-	-
Lenartz et al. (1996)	-	?	-	-	-	-	-
Longhi et al. (2014)	+	+	-	-	-	+	-
Piao et al. (2004)	+	?	-	-	+	+	-
Semiglasov et al. (2004)	+	+	+	-	+	+	-
Semiglasov et al. (2006)	+	+	+	-	-	+	-
Steuer-Vogt et al. (2001)	+	+	-	-	+	+	+
Steuer-Vogt et al. (2006)	+	+	-	-	-	+	+
Troger et al. (2009), (Troger et al. 2012)	+	+	-	-	-	+	-
Troger et al. (2016), Troger et al. (2014b)	+	+	-	-	-	+	-
Troger et al. (2013)	+	+	-	-	+	+	-
Troger et al. (2014a)	+	+	-	-	-	+	-

RSQ Random sequence generation, AC allocation concealment, BPP blinding of participants/personnel, BOA blinding of outcome assessment, IOD incomplete outcome data, SR = selective reporting, OSB other sources of Bias; low risk of Bias +, unclear risk of Bias ?, high risk of Bias -

unclear risk of selection bias because of missing information about random sequence generation (3 studies) and/or allocation concealment (6 studies).

Second, performance bias (i.e. systematic differences between treatment and control group in care or in exposure to other factors than analyzed as intervention) and detection bias (i.e. systematic differences between groups in determination of outcomes) was found in every study. No study was blinded with the exception of Semiglasov 2004 and 2006 in which according to the authors at least for the professionals the blinding did not worked.

Third, criteria for a strong bias for systematic differences between groups due to dropout (i.e. attrition bias) were fulfilled in 14 of the studies. In four studies there was an unclear risk of attrition bias and in six only a small risk existed.

Finally, in most of the studies, there was a low risk of reporting bias. That means the selective report of outcomes.

Apart from these risks, several other important risks of bias in the studies must be noted. First of all, another

risk of bias in 13 studies was the very small sample size (per arm less than 30 patients) independently from power analysis (Cazacu et al. 2003; El-Kolaly et al. 2016; Gaafar et al. 2014; Goebell et al. 2002; Grossarth-Maticek and Ziegler 2006b, 2007a, b, c, 2008; Kim et al. 2012; Lenartz et al. 2000; Longhi et al. 2014). On the one hand this makes statistical calculations less reliable or even impossible and on the other hand it reduces significantly the generalizability of results.

Further, in three studies less patients were included than was calculated in power analysis (Bar-Sela et al. 2013; Longhi et al. 2014; Troger et al. 2013). In these studies, there is a risk that no significant results were detected in spite of groups differing in reality. Apart from that, in 14 studies either no power analysis was conducted or it was not reported (Cazacu et al. 2003; El-Kolaly et al. 2016; Gaafar et al. 2014; Goebell et al. 2002; Grossarth-Maticek and Ziegler 2006a, b, 2007a, b, c, 2008; Heiny and Albrecht 1997; Lenartz et al. 1996, 2000; Piao et al. 2004).

Additionally, multiple testing increased the probability that at least one significant result appeared although in reality there was no difference between study arms. In many studies, especially regarding QoL, many single tests were conducted without controlling for multiple testing. Especially, in case of only few significant outcomes, these results might be due to multiple testing.

In some studies, there was an unclear therapeutic setting. In 8 studies both conventional and mistletoe treatment setting were not described in detail (Grossarth-Maticek and Ziegler 2006a, b, 2007a, b, c, 2008). Further, in one study, patients with pancreatic cancer of advanced stage received individual best supportive care in control and mistletoe group (Troger et al. 2013, 2014a). As this palliative treatment was not described at all, it cannot be excluded that there were systematic differences between treatment and control group which had influence on outcome parameter.

Overall, in at least 16 studies there was an unclear risk of bias due to bad reporting quality in general (Cazacu et al. 2003; El-Kolaly et al. 2016; Gaafar et al. 2014; Goebell et al. 2002; Grossarth-Maticek and Ziegler 2006a, b, 2007a, b, c, 2008; Heiny and Albrecht 1997; Lenartz et al. 1996, 2000; Longhi et al. 2014; Piao et al. 2004).

Finally, it is seen as a risk of Bias that there are many studies which, respectively, were written by the same group of authors or several studies even refer, respectively, to a one cohort of patients. There is a high probability that results of different studies from the same group of authors are not independently of each other.

### Survival and morbidity analysis

Overall survival was analyzed in 14 studies (Table 4). Of these, five found positive effects of mistletoe treatment on OS in breast cancer (Grossarth-Maticek and Ziegler 2006b), colorectal cancer (Cazacu et al. 2003), advance staged Glioma (Lenartz et al. 2000), non-metastatic corpus-uteri cancer (Grossarth-Maticek and Ziegler 2008), and pancreatic cancer (Troger et al. 2013). Another nine studies did not report significant differences between treatment and control group in breast cancer (Grossarth-Maticek and Ziegler 2006a), colorectal cancer (Heiny and Albrecht 1997), majority of included gynecological cancers (Grossarth-Maticek and Ziegler 2007b, c, 2008), lung cancer (Bar-Sela et al. 2013) and melanoma (Grossarth-Maticek and Ziegler 2007a; Kleeberg et al. 2004).

Progression free survival, disease free survival or disease specific survival were examined in nine studies. In most of the studies there were no significant differences between treatment and control group (Goebell et al. 2002; Heiny and Albrecht 1997; Kleeberg et al. 2004; Lenartz et al. 2000; Steuer-Vogt et al. 2001; Troger et al. 2012, 2016). Only Longhi et al. (2014), Grossarth-Maticek

and Ziegler (2006a) and (Grossarth-Maticek and Ziegler 2007a) provided weak support for a positive effect of mistletoe treatment.

In two studies tumor response was analyzed. First, in Heiny and Albrecht (1997) 21.4% of patients treated with mistletoe extract and chemotherapy showed a complete and partial remission compared to 22.6% of patients treated with chemotherapy only. Second, in the study by Goebell et al. (2002) in mistletoe group as well as in control group, respectively, three patients (A: 13%, B: 14%) showed an increase of histopathological grade during study period of 3 years.

### Adverse events regarding mistletoe treatment

In 54% of all included studies adverse events of mistletoe supplements were reported (Bar-Sela et al. 2013; Gaafar et al. 2014; Goebell et al. 2002; Heiny and Albrecht 1997; Kim et al. 2012; Kleeberg et al. 2004; Longhi et al. 2014; Piao et al. 2004; Semiglasov et al. 2004; Semiglasov et al. 2006; Steuer-Vogt et al. 2001; Troger et al. 2009, 2013, 2014b), whereas in two studies no adverse event due to mistletoe supplement were reported (Goebell et al. 2002; Troger et al. 2009, 2013). Altogether, in most studies there were only mild and local reactions.

Five studies reported patients dropping out because of side effects of mistletoe treatment (Bar-Sela et al. (2013): one patient due to grade 2 local skin reaction, Gaafar et al. (2014): two patients due to allergic reactions, Kleeberg et al. (2004): five (4.9%) patients due to grade 3–4 toxicities; Semiglasov et al. (2004): five patients, reasons not reported (except one patient due to erythema), Steuer-Vogt et al. (2001): 16 patients in stratum A without additional radiotherapy (16%) and 27 patients in stratum B with radiotherapy (20%). In one study the authors explicitly wrote that no patients discontinued due to adverse events (Heiny and Albrecht 1997).

Adverse events (grading after Common Terminology Criteria of Adverse Events (v3.0) if documented):

*Skin reactions* Patients reported local skin reactions at injection site (mostly grade 1 or 2) in eight studies. The proportion of patients with this adverse event is reported between 6 and 59% (Bar-Sela et al. 2013; Heiny and Albrecht 1997; Kim et al. 2012; Longhi et al. 2014; Piao et al. 2004; Semiglasov et al. 2004; Semiglasov et al. 2006; Steuer-Vogt et al. 2001; Troger et al. 2014b).

Few generalized skin reactions such as pruritus or urticaria were found in five different studies [Semiglasov et al. (2004); Semiglasov et al. (2006)]: reddening and allergic skin reaction; Steuer-Vogt et al. (2001): prurigo, induration and vesiculation; Heiny and Albrecht (1997): induration. Piao et al. (2004) reported 1 case of angioedema and urticaria.

**Table 4** Effect of mistletoe treatment regarding survival of cancer patients

Study	Survival-morbidity-parameter	OS/PFS/DFS/tumor response
<b>Bladder cancer</b>		
Goebell et al. (2002)	DFS (18 months)	A: $n = 31$ , B: $n = 30$
	1. Number of recurrences	DFS (in months)
	2. Number without disease	1. A: 31, B: 30; ns
	3. Median DFS	A: 6.3, B: 6.4 ns
	Tumor response	2. A: 9, B: 9 ns
Number of patients with	3. A: 9, B: 10.5 ns	
Increase of histopathological grade	Tumor response	
	A: 3 (13%), B: 3 (14%)	
<b>Breast cancer</b>		
Grossarth-Maticek and Ziegler (2006a)	OS	A: $n = 38$ , B: $n = 38$
	HR (95% CI)	OS
	PFS	0.65 (0.34–1.25), $p = 0.2$
	HR (95% CI)	DFS
	1. Number of recurrences	1. 0.44 (0.14, 1.44), $p = 0.18$
	2. Number of lymphatic metastases (Median difference (95% CI) (years); proportional hazard assumption not fulfilled)	2. 1.88 (–0.21, 4.17), $p = 0.063$
	3. Number of distant metastases	3. 0.50 (0.24, 1.039), $p = 0.061$
	4. Number of 1–3	4. 0.65 (0.47–0.91), $p = 0.012$
Grossarth-Maticek and Ziegler (2006b)	OS	A: $n = 17$ , B: $n = 17$
	Median difference (95% CI) (years); proportional hazard assumption not fulfilled for this data set	2.5 (0.83, 4.50), no $p$ value
Troger et al. (2009, 2012, 2014b, 2016)	DFS (5 years)	Troger et al. (2012)
	1. Median (month)	A: $n = 28$ , B: $n = 29$
	2. DFS rate	1. Not calculated (recurrence/metastasis probability only 28%)
		2. A: 6/28, B: 8/29, $p = 0.551$
		Per intervention
		RTX: A: 4/19, B: 3/18, $p = 0.792$
		AHT: A: 4/18, B: 4/14, $p = 0.659$
		Troger et al. (2016)
	A: $n = 28$ , B: $n = 29$	
	1. Not calculated (recurrence/metastasis probability only 33%)	
	2. A: 19/28, B: 21/29, $p = 0.746$	
<b>Colorectal cancer</b>		
Cazacu et al. (2003)	OS	Stage C
	Median (days)	A: $n = 18$ , B: $n = 16$ , C: $n = 6$
		A: 757*, B: 547, C: 502
		Stage D
		A: $n = 15$ , B: $n = 5$ , C: $n = 8$
		Stage D: A: 505*, B: 214, C: 451
		(*sign. $p < 0.05$ )
Heiny and Albrecht (1997)	PFS: Unclear if median or mean (weeks)	A: $n = 38$ , B: $n = 41$
	OS: Unclear if median or mean (weeks)	PFS: A: 30.8, B: 31.2 ns
	Tumor response: complete and partial remission (%)	OS: A: 50, B: 52.8 ns
		Tumor response
		A: 21.4, B: 22.6
<b>Glioma</b>		
Lenartz et al. (2000)	OS: Mean (50 months)	A: $n = 20$ , B: $n = 18$
	1. All patients	OS
	2. Stage III/IV	1. A: $21.71 \pm 3.7$ ; B: $17.32 \pm 3.9$ ns
	DFS: Mean (50 months)	2. A: $20.05 \pm 3.5$ ; B: $9.90 \pm 2.1$ , $p = 0.035$
	1. all patients	DFS
	2. Stage III/IV	1. A: $14.41 \pm 2.7$
	B: $14.76 \pm 3.6$ , no $p$ value	
	2. A: $17.43 \pm 8.2$ ; B: $10.45 \pm 3.9$ , no $p$ value	

**Table 4** (continued)

Study	Survival-morbidity-parameter	OS/PFS/DFS/tumor response
<b>Head and neck cancer</b>		
Steuer-Vogt et al. (2001, 2006)	1. DFS (4 years) 2. DSS (4 years) hazard ratios (95% CI)	A: $n = 235$ , B: $n = 242$ 1. 0.88 (0.63 ± 1.21) ns 2. 0.96 (0.66 ± 1.38) ns
<b>Lung cancer</b>		
Bar-Sela et al. (2013)	OS + PFS Median (months)	A: $n = 33$ , B: $n = 39$ OS: Stage III: A: 15.9, B: 13.3 $p = ns$ ; Stage IV: A: 8.3; B: 8.9, $p = ns$ PFS: A: 6; B: 4.8, $p = ns$
<b>Melanoma</b>		
Grossarth-Maticek and Ziegler (2007a)	OS (years) Hazard ratios (95% CI) PFS (years) 1. Time to recurrence, lymph node metastases, distant metastases 2. Time to brain metastases Hazard ratios (95% CI)	A: $n = 22$ , B: $n = 22$ OS 0.47 (0.19, 1.14), $p = 0.096$ PFS 1. 0.49 (0.32, 0.75) significant, $n$ not reported 2. 0.50 (0.09, 2.73), ns ( $n$ not reported)
Kleeberg et al. (2004)	DFS + OS hazard ratios (95% CI) and $p$ value (Wald test)	A: $n = 102$ , B: $n = 102$ Multivariate analysis (treatment, stage/number of positive lymph nodes) DFS: 1.34 (0.95, 1.91), $p = 0.10$ OS: 1.27 (0.87, 1.84) $p = 0.2$
<b>Osteosarcoma</b>		
Longhi et al. (2014)	DFS 1. Post relapse DFS (12 months) rate versus 12% (rate of previous studies without treatment) 2. Median (month)	A: $n = 9$ , B: $n = 11$ 1. Arm A: 55.6 [21.2; 86.3] vs 12%, $p = 0.0041$ Arm B: 27.3 [6.0, 61.0] vs 12%, $p = 0.2724$ 2. A: 39 (Range 2–73), B: 4 (Range 1–47)
<b>Other gynecological cancers</b>		
<b>Cervical cancer</b>		
Grossarth-Maticek and Ziegler (2007b)	OS Median difference (95% CI) (years)	A: $n = 19$ , B: $n = 19$ 0.44 (−0.17–1.00), $p = 0.16$
<b>Corpus uteri cancer</b>		
Grossarth-Maticek and Ziegler (2008)	OS Median difference (95% CI) (years)	No metastases A: $n = 30$ , B: $n = 30$ 1.50 (0.46, 2.58), $p = 0.005$ Metastases A: $n = 26$ , B: $n = 26$ 0.08 (−0.46, 1.92), $p = 0.78$
<b>Ovarian cancer</b>		
Grossarth-Maticek and Ziegler (2007c)	OS Median difference (95% CI, only figure) (years)	No metastases A: $n = 21$ , B: $n = 21$ 1.46 (ca. 0.25, 5.3), $p = 0.012$ Metastases A: $n = 20$ , B: $n = 20$ 1.38 (ca. 0.5, 3.5), $p = 0.001$
<b>Pancreatic cancer</b>		
Troger et al. 2013	OS (12 months) Median (months), hazard ratios (95% CI) 1. All patients 2. Subgroup analysis	A: $n = 110$ , B: $n = 110$ 1. A: 4.8, B: 2.7, HR: 0.49 [0.36–0.65] $p < 0.0001$ 2. bad prognosis (at least 2 criteria: UICC = IV, age > 65, ECOG ≥ 2) A: 3.4, B: 2.0, HR: 0.55 [0.37–0.82], $p < 0.0031$ Good Prognosis A: 6.6, B: 3.2, HR: 0.43 [0.28–0.65], $p < 0.0001$ No group Multiple testing problem, high risk of attrition bias

AHT hormone therapy, DFS disease free survival, DSS disease-specific survival, HR hazard ratio, ns no significant differences, OS Overall survival, PFS progression free survival, RTX radiotherapy

*Other adverse events* Few cases of fever appeared in 4 studies (Gaafar et al. 2014; Heiny et al. 1998; Piao et al. 2004; Steuer-Vogt et al. 2001).

The remaining adverse events per included studies were grade one chills, headache, malaise and two cases of allergic reactions which did not require hospitalization (Gaafar et al. 2014), one case of hypotension (Longhi et al. 2014), respectively, one case of chest pain, myalgia, dizziness and diarrhea (Kim et al. 2012), chill and muscle pain, allergic conjunctivitis and headache (Semiglasov et al. 2004), few cases of melalgia, sleeplessness, tiredness, coldness or heat sensation and sneezing (Steuer-Vogt et al. 2001) and one case of grade 2 rhino-conjunctivitis in one eye (Troger et al. 2014b).

### Potentially serious adverse events

Overall, 27 serious adverse events were reported, from that three were attributed to the mistletoe treatment:

- Kim et al. (2012): one case of post-operative bleeding and one case of an acute infection (not specified), both in the treatment group and not attributed to mistletoe.
- Longhi et al. (2014): three cases (two mistletoe, one etoposide patient) of patients for surgery (not specified) and two cases of pneumonia (both etoposide patients). Pneumonias were not attributed to mistletoe.
- Semiglasov et al. (2004): After withdrawal of the study medication, one patient of the mistletoe group developed an ulcerous necrotic enterocolitis, a febrile neutropenia and an infectious toxic shock syndrome and died. This case was not attributed to the mistletoe treatment.
- Semiglasov et al. (2006): one patient of the mistletoe group developed an acute otitis, which was not attributed to the mistletoe treatment. In the placebo group, one patient developed a febrile neutropenia and one patient developed diabetes mellitus.
- Troger et al. (2013): one case of cerebral infarction not attributed to the mistletoe treatment.
- Piao et al. (2004): 15 cases (5 in the mistletoe group and 10 in the control group). In the mistletoe group, one case of angioedema allocated to mistletoe and for the remaining four cases not attributed to mistletoe no further information was provided. In the control group no case was specified.

## Discussion

As in earlier systematic reviews (Bussing et al. 2012; Ernst et al. 2003; Horneber et al. 2008; Kienle et al. 2009; Kienle and Kiene 2007, 2010; Lange-Lindberg et al. 2006; Melzer et al. 2009; Ostermann and Bussing 2012; Ostermann et al.

2009), studies varied regarding cancer type and stages (i.e. there are almost no studies including the same histopathology), therapeutic setting regarding main intervention and mistletoe treatment, sample size and methodological quality. The endpoints were survival, side effects of cancer treatments, quality of life and adverse events due to mistletoe therapy.

In most of included studies, authors might have or most probably have a strong conflict of interest as funding was in from pharmaceutical companies in six publications (Cazacu et al. 2003; Kim et al. 2012; Semiglasov et al. 2004; Semiglasov et al. 2006; Troger et al. 2014b, 2016) or from societies dedicated to Anthroposophical Medicine even in twelve publications (Grossarth-Maticcek and Ziegler 2006a, b, 2007a, b, c, 2008; Troger et al. 2009, 2012, 2013, 2014a, b, 2016). Apart from that in another three articles there was no information about conflict of interests (Goebell et al. 2002; Heiny and Albrecht 1997; Piao et al. 2004).

Furthermore, one-third of the 28 included publications were conducted by two groups of authors (Grossarth-Maticcek and Ziegler 2006a, b, 2007a, b, c, 2008; Troger et al. 2009, 2012, 2013, 2014a, b, 2016), which reduces validity and generalizability of the results of this systematic review. These studies could not be seen independently of each other. In all studies of Grossarth and Ziegler the patients were derived of a huge cohort of German cancer patients who were recruited 1973–1988 and all studies of Troger et al. were conducted in Belgrad. For example while Troger et al. in (2013) stressed the unbiased approach of the physicians in charge of the study in Serbia due to no former experience in mistletoe treatment, the study was conducted at the same hospital as the study reported formerly (Troger et al. 2009).

### Efficacy of mistletoe treatment regarding survival and morbidity

As our analysis shows, the majority of studies did not show any effect of mistletoe on survival. Especially high quality studies do not show any benefit. These results are analogous to Horneber et al. (2008) and Lange-Lindberg et al. (2006).

Progression free, disease free or disease specific survival were investigated in nine studies. In accordance with the data on overall survival, almost no significant differences between treatment and control group were found. Furthermore, mistletoe seems to have no effect on tumor response according to the two included studies analyzing this endpoint (Goebell et al. 2002; Heiny and Albrecht 1997).

### Adverse events of mistletoe treatment

Mistletoe therapy is reported to have only few and minor side effects (Steele et al. 2014). Yet, as only adverse effects ascribed to the mistletoe treatment are included

in the reports of the studies, so far, no comprehensive data exist. In fact, interactions might stem from immunostimulation. For this reason, some experts exclude patients with leukemia and lymphoma as well as those with brain tumors or brain metastases from treatment. Furthermore, in vitro data point to a stimulation of tumor growth for lymphoma, renal cell carcinoma and melanoma (Thies et al. 2005). The study by Kleeberg et al. (2004) has been intensely discussed and criticized from proponents of Anthroposophic Medicine. In fact, this study depicts a possible raise in risk of metastases, yet, data were not significant. Considering a low evidence of benefit with a possible risk, the recommendation against mistletoe in “immunologic” cancers seems sound. These data are supported by laboratory data and case reports (Styczynski and Wysocki 2006).

In this context, discussion is open whether mistletoe might increase allergic reactions in patients with allergies or immune reactions on cancer drugs. Anaphylactic reactions to mistletoe are described rarely (Hagenah et al. 1998; Hutt et al. 2001; Shaw et al. 2004). Yet, patients on cancer drugs with a potential to induce sensitivity reactions as oxaliplatin, taxanes or antibodies may have an increased risk of these reactions (Hubner and Phieler 2009). One argument against this risk is the lack of respective publications. Yet, as most patients do not disclose using complementary medicine to their oncologist (Robinson and McGrail 2004; Saxe et al. 2008) and as most oncologists do not rate complementary medicine as potentially risky (Conrad et al. 2014; Henf et al. 2014; Ott et al. 2015; Trimborn et al. 2013) under-reporting is most probable. This under-reporting may also be valid for other side effects of mistletoe and interactions. In the study by Semiglasov et al. (2004), a serious adverse event with an ulcerous necrotic enterocolitis, a febrile neutropenia and an infectious toxic shock syndrome with consecutive death was described but judged not being related to the study medication by the investigator and the pharmacological committee. Moreover, in 2017 a group of authors from Anthroposophy reported that they did not find any negative interactions between immunological therapies and mistletoe (Thronicke et al. 2017). Yet, they only reported data from small cohort of 16 patients on [Nivolumab (75%), Ipilimumab (19%) or Pembrolizumab (6%)] form which only nine additionally received *Viscum album*. As serious adverse events from these immunological therapies are rare, this report of a small case series does not provide any scientific information on the risk of the combination.

Last but not least, interactions may also stem from inadvertent sides. Abreu et al. (2017) report on a false positive PET-CT after the injection of mistletoe by a patient with Hodgkin lymphoma.

## Limitations of this work

Several limitations of this systematic review have to be mentioned. First, we only included randomized controlled studies. Information from well-described case reports, case series and cohorts were not assessed systematically. Second, we focused on adults, omitting literature on children. Third, due to the heterogeneity of considered RCTs no meta-analysis could be conducted, and no moderators of mistletoe treatment be determined. Finally, this review focused on more recent mistletoe literature and exclude articles publicized earlier than 1995.

## Conclusion

Most studies did not show any effect of mistletoe on survival. Especially high quality studies do not show any benefit. There are some arguments to assume that genuine side effects from mistletoe or interactions with conventional therapy may not be reported adequately in studies and not even noticed in regular cancer care. Accordingly, the benefit-risk-assessment for mistletoe is difficult and no evidence-based indications can be stated today. Physicians should not prescribe mistletoe in case of leukemia, lymphoma or renal cancer and melanoma. Furthermore, interactions with cancer drugs should be avoided and more attention should be paid to reporting possible interaction in scientific publications.

**Acknowledgements** The authors want to thank Dajana Daum, Catalina Hoppe, Gunnar Voß and Louisa Wortmann for supporting in data extraction/data management and duplicate search.

**Funding** The work of MF was funded in parts (search of the literature, title-abstract screening) by the German Guideline “S3 Leitlinie Komplementärmedizin in der Behandlung von onkologischen PatientInnen (Registernummer 032–055OL)” funded by the German Cancer Aid (Fördernummer 11583) within the German Guideline Program in Oncology. Furthermore, the work of MF was funded in parts (evidence table) by the working group Prevention and Integrative Oncology of the German Cancer Society.

## Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interest.

## References

- Abreu P, Sanchez R, Mut T, Balaguer D, Latorre I, Rodriguez H (2017) Homeopathic mistletoe adverse reaction mimics nodal involvement in 18F-FDG PET/CT performed for evaluation of response to chemotherapy in lymphoma. *Revista Espanola de Medicina Nuclear e Imagen Molecular* 36:110–112. <https://doi.org/10.1016/j.rem.2016.07.005>
- Bar-Sela G, Wollner M, Hammer L, Agbarya A, Dudnik E, Haim N (2013) Mistletoe as complementary treatment in patients with

- advanced non-small-cell lung cancer treated with carboplatin-based combinations: a randomised phase II study. *Eur J Cancer* 49:1058–1064
- Bussing A, Raak C, Ostermann T (2012) Quality of life and related dimensions in cancer patients treated with mistletoe extract (iscador): a meta-analysis. *Evid Based Complement Altern Med eCAM* 2012. <https://doi.org/10.1155/2012/219402>
- Cazacu M et al (2003) The influence of isorel on the advanced colorectal cancer. *Cancer Biother Radiopharm* 18:27–34
- Conrad AC, Muenstedt K, Micke O, Prott FJ, Muecke R, Huebner J (2014) Attitudes of members of the German Society for Palliative Medicine toward complementary and alternative medicine for cancer patients. *J Cancer Res Clin Oncol* 140:1229–1237. <https://doi.org/10.1007/s00432-014-1656-9>
- El-Kolaly RM, Abo-Elnasr M, El-Guindy D (2016) Outcome of pleurodesis using different agents in management of malignant pleural effusion Egyptian. *J Chest Dis Tuberc* 65:435–440
- Ernst E, Schmidt K, Steuer-Vogt MK (2003) Mistletoe for cancer? A systematic review of randomised clinical trials. *Int J Cancer* 107:262–267
- Gaafar R, Abdel Rahman ARM, Aboukaseem F, El Bastawisy A (2014) Mistletoe preparation (*Viscum Fraxini-2*) as palliative treatment for malignant pleural effusion: a feasibility study with comparison to bleomycin. *Ecancermedicalscience* 8:424. <https://doi.org/10.3332/ecancer.2014.424>
- Goebell PJ, Otto T, Suhr J, Rubben H (2002) Evaluation of an unconventional treatment modality with mistletoe lectin to prevent recurrence of superficial bladder cancer: a randomized phase II trial. *J Urol* 168:72–75
- Grossarth-Maticsek R, Ziegler R (2006a) Prospective controlled cohort studies on long-term therapy of breast cancer patients with a mistletoe preparation (Iscador). *Forschende Komplementarmedizin* (2006) 13:285–292
- Grossarth-Maticsek R, Ziegler R (2006b) Randomised and non-randomised prospective controlled cohort studies in matched-pair design for the long-term therapy of breast cancer patients with a mistletoe preparation (Iscador): a re-analysis. *Eur J Med Res* 11:485–495
- Grossarth-Maticsek R, Ziegler R (2007a) Efficacy and safety of the long-term treatment of melanoma with a mistletoe preparation (Iscador). *Schweizerische Zeitschrift fur GanzheitsMedizin [German]* 19:325–332
- Grossarth-Maticsek R, Ziegler R (2007b) Prospective controlled cohort studies on long-term therapy of cervical cancer patients with a mistletoe preparation (Iscador) *Forschende Komplementarmedizin* (2006) 14:140–147
- Grossarth-Maticsek R, Ziegler R (2007c) Prospective controlled cohort studies on long-term therapy of ovarian cancer patients with mistletoe (*Viscum album L.*) extracts iscador. *Arzneimittelforschung* 57:665–678
- Grossarth-Maticsek R, Ziegler R (2008) Randomized and non-randomized prospective controlled cohort studies in matched pair design for the long-term therapy of corpus uteri cancer patients with a mistletoe preparation (Iscador). *Eur J Med Res* 13:107–120
- Grossarth-Maticsek R, Kiene H, Baumgartner SM, Ziegler R (2001) 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* 7:57–66 (68–72, 74–56 passim)
- Hagenah W, Dorges I, Gafumbegete E, Wagner T (1998) Subcutaneous manifestations of a centrocytic non-Hodgkin lymphoma at the injection site of a mistletoe preparation. *Deutsche medizinische Wochenschrift* (1946) 123:1001–1004 <https://doi.org/10.1055/s-2007-1024111>
- Heiny BM, Albrecht V (1997) Complementary modes of therapy with mistletoe lectin-1. *Medizinische Welt [German]* 48:419–423
- Heiny BM, Albrecht V, Beuth J (1998) Correlation of immune cell activities and beta-endorphin release in breast carcinoma patients treated with galactose-specific lectin standardized mistletoe extract. *Anticancer Res* 18:583–586
- Henf A, Wesselmann S, Huthmann D, Muenstedt K, Huebner J, On behalf of the Working Group P, Intergrative Oncology of the German Cancer Society J (2014) Complementary and alternative medicine in German Cancer Centers. *Oncol Res Treat* 37:390–394. <https://doi.org/10.1159/000364897>
- Higgins JPT, Altman DG, Sterne JAC (2017) Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (eds) *Cochrane Handbook for Systematic Reviews of Interventions* version 5.2.0 (updated June 2017). Cochrane
- Horneber MA, Bueschel G, Huber R, Linde K, Rostock M (2008) Mistletoe therapy in oncology *Cochrane Database of Syst Rev* 107:CD003297
- Hubner J, Phielier F (2009) Hypersensitivity reaction to oxaliplatin recurrence during mistletoe therapy? *Tumor Diagnostik Therapie [German]* 30:36–39
- Huebner J (2008) *Komplementäre Onkologie - Supportive Maßnahmen und evidenzbasierte Empfehlungen*. Schattauer, Stuttgart
- Hutt N, Kopferschmitt-Kubler M, Cabalion J, Purohit A, Alt M, Pauli G (2001) Anaphylactic reactions after therapeutic injection of mistletoe (*Viscum album L.*). *Allergologia et immunopathologia* 29:201–203
- Kienle GS, Kiene H (2007) Complementary cancer therapy: a systematic review of prospective clinical trials on anthroposophic mistletoe extracts. *Eur J Med Res* 12:103–119
- Kienle GS, Kiene H (2010) Review article: Influence of *Viscum album L* (European mistletoe) extracts on quality of life in cancer patients: a systematic review of controlled clinical studies. *Integr Cancer Ther* 9:142–157
- Kienle GS, Glockmann A, Schink M, Kiene H (2009) *Viscum album L.* extracts in breast and gynaecological cancers: a systematic review of clinical and preclinical research. *J Exp Clin Cancer Res* 28:79
- Kim KC, Yook JH, Eisenbraun J, Kim BS, Huber R (2012) Quality of life, immunomodulation and safety of adjuvant mistletoe treatment in patients with gastric carcinoma—a randomized, controlled pilot study. *BMC Complement Altern Med* 12:172
- Kleeberg UR et al (2004) Final results of the EORTC 18871/DKG 80-1 randomised phase III trial. rIFN-alpha2b versus rIFN-gamma versus ISCADOR M versus observation after surgery in melanoma patients with either high-risk primary (thickness > 3 mm) or regional lymph node metastasis. *Eur J Cancer* 40:390–402
- Lange-Lindberg A-M, Velasco Garrido M, Busse R (2006) Mistletoe treatments for minimising side effects of anticancer chemotherapy. *GMS Health Technol Assess* 2:Doc18
- Lenartz D, Stoffel B, Menzel J, Beuth J (1996) Immunoprotective activity of the galactoside-specific lectin from mistletoe after tumor destructive therapy in glioma patients. *Anticancer Res* 16:3799–3802
- Lenartz D, Dott U, Menzel J, Schierholz JM, Beuth J (2000) Survival of glioma patients after complementary treatment with galactoside-specific lectin from mistletoe. *Anticancer Res* 20:2073–2076
- Longhi A, Reif M, Mariani E, Ferrari S (2014) a randomized study on postrelapse disease-free survival with adjuvant mistletoe versus oral etoposide in osteosarcoma patients. *Evid Based Complement Altern Med eCAM* 2014. <https://doi.org/10.1155/2014/210198>
- Melzer J, Iten F, Hostanska K, Saller R (2009) Efficacy and safety of mistletoe preparations (*Viscum album*) for patients with cancer diseases. A systematic review. *Forschende Komplementarmedizin* (2006) 16:217–226
- Ostermann T, Bussing A (2012) Retrolective studies on the survival of cancer patients treated with mistletoe extracts: a meta-analysis. *Explore J Sci Heal* 8:277–281

- Ostermann T, Raak C, Bussing A (2009) Survival of cancer patients treated with mistletoe extract (Iscador): a systematic literature review. *BMC Cancer* 9:451
- Ott IM et al (2015) Attitude of oncology/hematology nurses from German speaking countries towards complementary and alternative medicine. *Trace Elem Electrolytes* 32:74–80
- Piao BK, Wang YX, Xie GR, Mansmann U, Matthes H, Beuth J, Lin HS (2004) 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* 24:303–309
- Robinson A, McGrail MR (2004) Disclosure of CAM use to medical practitioners: a review of qualitative and quantitative studies. *Complement Ther Med* 12:90–98. <https://doi.org/10.1016/j.ctim.2004.09.006>
- Saxe GA, Madlensky L, Kealey S, Wu DP, Freeman KL, Pierce JP (2008) Disclosure to physicians of CAM use by breast cancer patients: findings from the Women's Healthy Eating and Living Study. *Integr Cancer Ther* 7:122–129. <https://doi.org/10.1177/1534735408323081>
- Schierholz JM et al (2003) Complementary cancer therapy with standardized mistletoe extracts. Results of a controlled prospective multicentric randomized clinical trial. [German] *Deutsche Zeitschrift für Onkologie* 35:186–194
- Schink M et al (2007) Mistletoe extract reduces the surgical suppression of natural killer cell activity in cancer patients. a randomized phase III trial. *Forschende Komplementärmedizin* (2006) 14:9–17
- Semiglasov VF, Stepula VV, Dudov A, Lehman W, Mengs U (2004) 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* 24:1293–1302
- Semiglasov VF, Stepula VV, Dudov A, Schmitker J, Mengs U (2006) 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* 26:1519–1529
- Shaw HS, Hobbs KB, Kroll DJ, Seewaldt VL (2004) Delayed-type hypersensitivity reaction with iscador M given in combination with cytotoxic chemotherapy. *J Clin Oncol* 22:4432–4434. <https://doi.org/10.1200/jco.2004.04.140>
- Steele ML, Axtner J, Happe A, Kroz M, Matthes H, Schad F (2014) Adverse drug reactions and expected effects to therapy with subcutaneous mistletoe extracts (*Viscum album* L.) in cancer patients. *Evid Based Complement Altern Med eCAM* 2014. <https://doi.org/10.1155/2014/724258>
- Steuer-Vogt MK et al (2001) The effect of an adjuvant mistletoe treatment programme in resected head and neck cancer patients: a randomised controlled clinical trial European. *J Cancer* 37:23–31
- Steuer-Vogt MK, Bonkowsky V, Scholz M, Fauser C, Licht K, Ambrosch P (2006) Influence of ML-1 standardized mistletoe extract on the quality of life in head and neck cancer patients. *Hno* 54:277–286
- Styczynski J, Wysocki M (2006) Alternative medicine remedies might stimulate viability of leukemic cells. *Pediatr Blood Cancer* 46:94–98. <https://doi.org/10.1002/psc.20513>
- Thies A, Nügel D, Pfüller U, Moll I, Schumacher U (2005) Influence of mistletoe lectins and cytokines induced by them on cell proliferation of human melanoma cells in vitro. *Toxicology* 207:105–116. <https://doi.org/10.1016/j.tox.2004.09.009>
- Thronicke A, Steele M, Grah C, Matthes B, Schad F (2017) Clinical safety of combinational therapy of immune checkpoint inhibitors and *Viscum album* L. in patients with advanced or metastasized cancer. *Journal of Thorac Oncol* 12(1 Supplement 1):S1295–S1296
- Trimborn A et al (2013) Attitude of employees of a university clinic to complementary and alternative medicine in oncology. *Ann Oncology* 24:2641–2645. <https://doi.org/10.1093/annonc/mdt299>
- Troger W (2011) Connection between quality of life and neutropenia in breast cancer patients who were solely treated with chemotherapy or additionally with mistletoe therapy: results of a randomized study. *Deutsche Zeitschrift für Onkologie [German]* 43:58–67
- Troger W, Jezdic S, Zdravle Z, Tisma N, Hamre HJ, Matijasevic M (2009) Quality of life and neutropenia in patients with early stage breast cancer: a randomized pilot study comparing additional treatment with mistletoe extract to chemotherapy alone. *Breast Cancer Basic Clin Res* 3:35–45
- Troger W, Zdravle Z, Stankovic N, Matijasevic M (2012) Five-year follow-up of patients with early stage breast cancer after a randomized study comparing additional treatment with *Viscum album* (L.) extract to chemotherapy alone. *Breast Cancer Basic Clin Res* 6:173–180. <https://doi.org/10.4137/BCBCR.S10558>
- Troger W, Galun D, Reif M, Schumann A, Stankovic N, Milicevic M (2013) *Viscum album* [L.] extract therapy in patients with locally advanced or metastatic pancreatic cancer: a randomised clinical trial on overall survival European. *J Cancer* 49:3788–3797
- Troger W, Galun D, Reif M, Schumann A, Stankovic N, Milicevic M (2014a) Quality of life of patients with advanced pancreatic cancer during treatment with mistletoe: a randomized controlled trial. *Deutsch Arzteblatt Int* 111:493–502
- Troger W, Zdravle Z, Tisma N, Matijasevic M (2014b) Additional therapy with a mistletoe product during adjuvant chemotherapy of breast cancer patients improves quality of life: an open randomized clinical pilot trial. *Evid Based Complement Altern Med eCAM* 2014. <https://doi.org/10.1155/2014/430518>
- Troger W, Zdravle Z, Stankovic N (2016) Five-Year follow-up of patients with early stage breast cancer after a randomized study with *Viscum album* (L.) extract. [German]. *Deutsche Zeitschrift für Onkologie* 48:105–110
- Tröger W, Galun D, Reif M, Schumann A, Stankovi N, Miličević M (2013) *Viscum album* [L.] extract therapy in patients with locally advanced or metastatic pancreatic cancer: a randomised clinical trial on overall survival. *Eur J Cancer (Oxford Engl 1990)* 49:3788–3797. <https://doi.org/10.1016/j.ejca.2013.06.043>
- Tröger W, Galun D, Reif M, Schumann A, Stankovi N, Miličević M (2014) Quality of life of patients with advanced pancreatic cancer during treatment with mistletoe: a randomized controlled trial. *Deutsch Arzteblatt Int* 111:493–502. <https://doi.org/10.3238/arztebl.2014.0493>