Table: Mistletoe (*Viscum album*) for survival-related outcomes in cancer

Source: CAM-Cancer Collaboration. Mistletoe (*Viscum album*) [online document]. Mistletoe | Survival-related outcomes, October 2026.

Review characteristics	PICO of included studies	Results and conclusions	Assessment
Loef M, Walach H. Survival of Cancer Patients Treated with Non-Fermented Mistletoe Extract: A Systematic Review and Meta-Analysis. Integr Cancer Ther. 2022;21: 15347354221133561. (Loef 2022)			
Type of review and synthesis Systematic review with meta-analysis. **Included studies: n and design** 11 RCTs, 8 nRCTs **Search strategy** Databases: Embase, Pubmed, OpenGrey, CENTRAL, clinicaltrials.gov, and EuropePMC. Additionally hand searches, Google Scholar and VfK. Dates not stated. No restrictions. **Risk of bias assessment** RCTs: Cochrane RoB2 nRCTs: ROBINS I	**Included participants** 1629 patients (11 RCTs) and 2254 patients (8 nRCTs) with various cancers at various stages. **Intervention:** Unfermented mistletoe extract (uME): Eurixor (n=3), Helixor (n=5), Isorel, Lektinol, as adjuvant or sole treatment. **Control:** Conventional oncological treatment, ctx, rt, surgery; no (additional) treatment. Active non-oncological controls were considered only in sensitivity analyses. **Outcome measures:** OS, PFS, DFS or their corresponding time-to-event parameters. **Measure of treatment effect:** Hazard ratio and 95% CI for survival outcomes.	**Results for risk of bias assessment** RCTs: RoB2 8 some concerns, 3 high RoB, due mostly to deviations from intended interventions and selection of the reported result bias. nRCTss: ROBINS I all serious RoB mostly because of bias due to confounding (none critical). **Certainty of evidence** No GRADE or other formal assessment **Results for outcome measures** Statistically significant ($P \leq 0.05$) survival benefit for cancer patients treated with uME. Only trials without active control were included in overall MA. When included, effect estimates were no longer significant. **Overall survival** RCTs: HR = 0.81 (0.69-0.95, P=0.01 NRSIs: HR = 0.63 (0.4-1.01), P=0.05 **Adverse events** Not assessed. **Conclusions:** "*In light of a moderate to serious risk of bias, we found that uME may have a positive impact on survival of cancer patients. High quality RCTs are necessary to substantiate our results*."	**Quality of SR** Moderate to high according to AMSTAR2. **Comments** Substantial clinical heterogeneity of included studies. Multiple sources of heterogeneity explored in subgroup analysis. Use of surrogate measures RR and PFD for OS. Small number of included trials, all at high risk of bias or some concerns. Safety not reported. **Funding:** Förderverein komplementärmedizinische Forschung*, Arlesheim, Switzerland. **Competing interests:** No conflicts of interest declared. *Association for the promotion of complementary medicine research (not official translation).

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Ostermann T, Appelbaum S, Poier D, Boehm K, Raak C, Büssing A. A Systematic Review and Meta-Analysis on the Survival of Cancer Patients Treated with a Fermented Viscum album L. Extract (Iscador): An Update of Findings. Complement Med Res. 2020;27(4):260-271. Ostermann 2020

Type of review and synthesis
SR with meta-analysis, update of previous SR published in 2009.

Included studies: n and design
32 studies with 55 strata.
13 RCTs, 19 nRCTs.
24 had a prospective design, 2 a retrolective design, and 12 a retrospective design.
8 studies (all by the same first author) used a matched-pair design.

Search strategy
Databases:
PubMed/Medline, Embase, Cochrane Library/Cochrane CENTRAL, AMED, CAMbase and Scopus. Database of the journal *Der Merkurstab*.
Dates: Inception to Feb 2016.
Restrictions: German and English only.

Risk of bias / quality assessment
RCTs: Cochrane RoB
nRCTs: Newcastle Ottawa Scale (NOS).

Included studies and participants
Total of 13,745 patients. Cancer patients, all tumour entities and stages.

Interventions
Fermented mistletoe extracts: Iscador as adjuvant or sole treatment. Administered subcutaneously.

Controls
No details provided. As per inclusion criteria, control groups without Iscador (e.g., best supportive care, conventional therapies alone, observation); matched designs where applicable.

Outcome measures
Parameters associated with general and event-free survival (DFS, PFS, RFS, or time to these events).

Measure of treatment effect: HR CI 95% for overall or event-free survival. If HRs were not reported, they were estimated (e.g., from median/mean survival or 5-year survival rates) under an exponential survival assumption.

Results for risk of bias assessment
Overall, across trials and across domains, there was a small to medium risk of bias.
RCTs (Cochrane RoB): performance bias high risk due to unblinding. Detection bias: unlikely in OS study but in event-free survival outcomes. ;
Other domains judged as low risk.
nRCTs: Majority of the included studies (20/26) are of good quality (7-9 points on the NOS scale). Studies older than 40 years were of minor quality.

Certainty of evidence
No GRADE or other formal assessment.

Adverse events
Not assessed.

Results for outcome measures
The majority of studies reported positive effects in favour of Iscador. General survival HR of 0.59 (0.53, 0.65)], $p<0.0001$.

Subgroup analysis: Meta-regression did not reveal significant effects of sample size or study design. Significant differences between cancer entities in general survival, most pronounced effects in cervical (HR=0.43) and less pronounced in lung cancer (HR=0.84).

Conclusions:
"The data underline that adjuvant treatment of cancer patients with the mistletoe extract Iscador can be associated with a better survival. One may consider it as a second-line treatment, which may have distinct effectiveness in different tumour entities. Nevertheless, studies based on sound methodological designs and modern anti-tumour therapies are needed to establish the promising findings of studies published within more than 50 years."

Quality of SR
Low to moderate according to AMSTAR2.
No protocol registration of original SR 2009 nor this update.

Comments
Clinical heterogeneity of included studies.
Various subgroup and sensitivity analyses.
Control interventions or basic treatment not described.
Safety not reported.

Funding
Förderverein komplementärmedizinische Forschung, Arlesheim (Switzerland), provided financial support to perform this meta-analysis.

Competing interests
Two authors declared receiving funding from Förderverein komplementärmedizinische Forschung.

Note
Studies were excluded if control group also received the Iscador treatment, or when mistletoe extract preparations other than Iscador where also used.

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Peri-operative period

Cogo E, Elsayed M, Bhardwaj S, Cooley K, Aycho C, Liang V, Papadogianis P, Psihogios A, Seely D. Mistletoe Extracts during the Oncological Perioperative Period: A Systematic Review and Meta-Analysis of Human Randomized Controlled Trials. Curr Oncol. 2023 Sep 6;30(9):8196-8219.

Type of review and synthesis
SR with narrative synthesis and meta-analysis for mortality and recurrence.

Included studies: n and design
7 RCTs for efficacy analysis, RCTs and 3 cohort studies for safety.

Search strategy
Databases: MEDLINE, Embase, and Cochrane CENTRAL databases.
Dates: From inception to 14 January 2023
Restrictions: English language only.

Risk of bias assessment
RCTs: Cochrane RoB,
nRCTs: Newcastle Ottawa Scale

Included studies and participants
633 participants for efficacy analysis. Various cancers, patients undergoing cancer surgery during perioperative period (before, between and after surgery).

Interventions
Any included, Iscador, Isorel, Eurixor, lectin extract, not specified.

Control
No added treatment in 5 RCTs, active comparator in two. Concomitant conventional treatment (e.g. ctx, rt) was exclusion criterion.

Outcome measures
Survival: cancer recurrence, mortality, treatment response, stable disease, disease progression
Postoperative complications and infections
QoL: QoL measured with Karnofsky Performance Index; EORTC QLQ-C30.
AEs of mistletoe, reported narratively.

Measure of treatment effect
RR for binary outcomes mortality and recurrence.
MD for continuous outcomes.

Results for risk of bias assessment
RoB: Substantial RoB of bias was detected among all the included studies. 4 were of high RoB in at least one domain (mostly blinding bias), 3 of some concern, none low RoB.
nRCTs: Quality appraisal with NOS revealed a substantial risk of bias.

Certainty of evidence
No GRADE or other formal assessment.

Results for outcome measures
Survival (3 RCTs) and recurrence (3 RCTs): MA found no evidence for a difference between mistletoe extract and no added therapy for mortality and recurrence.

QoL (2 RCTs): One RCT reported QoL improvement.

Adverse events
AE definitions were often poorly described, and reporting was inconsistent across trials.
Two RCTs reported mistletoe extract discontinuations due to AEs and grade 3/4 toxicities. Nevertheless, no safety signals were detected from these 10 studies.

Conclusions:
Preliminary data are encouraging for mistletoe extracts, particularly in the context of colorectal cancer. However, the evidence is limited by the number of studies, an evaluation of different outcomes, and methodological limitations. Further high-quality research is warranted.

Quality of SR
Moderate to high according to AMSTAR2.

Comments
In contrast to other SRs, concomitant conventional treatment (i.e., chemotherapy, radiotherapy, etc.) with mistletoe was exclusion criterion.

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Competing interests
The authors declare no conflict of interest.

AE- adverse events
CI – confidence interval
Ctx, rt – chemotherapy, radiotherapy
DFS –disease free survival
HR – hazard ration
MA meta-analysis
MD – mean difference
ME – mistletoe extract
ME – mistletoe extract
NOS – Newcastle-Ottawa Scale
nRCT – non-randomized controlled trial
OS – overall survival
PFS – progression-free survival
PICOS - **P**opulation, **I**ntervention, **C**ontrol, **O**utcome, **S**tudies
RCT – randomized controlled trial
RoB Risk of bias
RR - relative risk
VfK – Verein fuer Krebsforschung

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Systematic reviews excluded from the evidence summary due to low quality

Freuding M, Keinki C, Micke O, Buentzel J, Huebner J. Mistletoe in oncological treatment: a systematic review : Part 1: survival and safety. J Cancer Res Clin Oncol. 2019 Mar;145(3):695-707. Freuding 2019			
Type of review and synthesis SR with narrative synthesis due to significant heterogeneity of interventions, outcomes, instruments. No synthesis plan described in methods. **Included studies: n and design** 24 RCTs (28 publications), survival assessed in 14 RCTs, progression or disease-free survival or tumour response in 10 RCTs. **Search strategy** Databases: Medline, Embase, Cochrane CENTRAL, PsycINFO, CINAHL and "Science Citation Index Expanded" (Web of Science). Dates: From 1995 to Oct 2017. Restrictions: Limited to English and German, full text only. **Risk of bias assessment** Cochrane RoB.	**Participants:** 2639 patients; survival (n=1054), progression- or disease-free survival or tumour response (n=1091) **Intervention** Any mistletoe extract, Iscador, Eurixor, Viscum-Fraxini, Lektinol, abnobaVISCUM, Isorel, "lectin extract"; as adjuvant or sole treatment. **Control** Conventional oncological treatment, ctx, rt, surgery; no (additional) treatment, active comparator; placebo. **Outcome measures** Overall survival, progression-free survival, disease-free survival, tumour response. Safety. **Measure of treatment effect** Number of studies reporting significant differences in above outcomes measures. Narrative description of adverse events.	**Risk of bias assessment** RoB* and SIGN checklist, latter not reported. Selection bias: 7 high, 6 unclear, 13 low Performance and detection bias "found in all studies". Attrition bias: 14 high, 4 unclear, 6 small. Reporting bias: "most studies low risk". Other RoB; very small sample sizes, underpowered studies, multiple testing, unclear therapeutic setting, multiple trials by same authors ie. not independent. **Results for outcome measures** Overall survival: of 14 studies 5 found positive effects, 9 did not report significant differences. High-quality studies did not show any benefit. PFS, DFS, DSS: of 9 studies, only 3 reported weak evidence for improvement, others no significant difference. Tumour response: no positive effects, worse than control. **Adverse events** Only few and minor side effects. Most were mild local injection site reactions. Several trials noted discontinuations due to AEs. Three serious AEs attributed to mistletoe. Safety has not been systematically assessed. **Conclusions** *"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."*	**Quality of SR** AMSTAR2 low. No protocol registration. No synthesis plan pre-defined. *Issues with RoB assessment. Survival outcomes typically have a lower risk across several domains, particularly measurement bias (performance and detection) and attrition, missing data. QoL outcomes are systematically more prone to bias due to their subjective nature and higher attrition. However, the authors conduct one RoB assessment independent of outcomes (survival part 1 vs QoL see part 2 below). **Comments** Restricted to literature published from 1995 onwards. Due to the considerable heterogeneity of considered RCTs, meta-analysis could not be conducted and no moderators of mistletoe treatment be determined. Low reporting quality of included studies. **Funding** Partly by the German Guideline "S3 Leitlinie Komplementärmedizin in der Behandlung von onkologischen PatientInnen" funded by the German Cancer Aid. Partly by the working group Prevention Integrative Oncology of the German Cancer Society. **Competing interests** The authors declare no conflict of interest

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