Concerted Action for Complementary and Alternative Medicine Assessment in the Cancer Field (CAM-Cancer) www.cam-cancer.org

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Mistletoe (Viscum album)

Abstract and key points

Extracts of mistletoe (*Viscum album)* are highly popular in cancer care, particularly in Europe. They are usually injected subcutaneously. Proponents of this therapy claim that it improves quality of life, strengthens the immune system, has a positive impact on tumour remission and survival of cancer patients. However, the evidence to support these claims is weak. Mistletoe is generally well tolerated and safe.

- Mistletoe preparations are used by many cancer patients.
- The main claims are that they prolong survival and increase quality of life.
- Numerous in-vitro data suggest anti-cancer activity.
- Non-randomised trials suggest effectiveness.
- The results of rigorous RCTs are, however, less convincing.
- There are no major safety issues.

What is it?

Scientific name / brand name / common name

Mistletoe (*Viscum album*) is a semiparasitic plant that grows throughout Europe, Asia and North Africa (North American mistletoe is a different species), most commonly on oak, chestnut, black poplar, and fruit trees. 1 It is also known as Birdlime, All-heal, or Viscum.

Brand names of various forms of mistletoe extract are ABNOBAViscum, Cephalektin, Eurixor®, Helixor®, Iscador®, Isorel, Lektinol™.

Ingredients

Mistletoe extracts contain pharmacologically active proteins (lectins). The composition of an extract may vary according to season, host tree, parts of the plant used and extraction method. Mistletoe extracts induce macrophage cytotoxicity, stimulate phagocytosis of immune cells, increase cytokine secretion and enhance cytotoxicity effects on various cell lines in vitro. 2-3 The plant also contains a host of other ingredients such as acids, alkaloids, amines, flavonoids, terpenoids and viscotoxins.

History / providers

Mistletoe has been used medicinally for centuries and has been employed to treat cancer, epilepsy, infertility, menopausal symptoms, nervous tension, asthma, hypertension, headache, and dermatitis. Recent interest in mistletoe began in the 1920s after it was first proposed for the treatment of cancer by Rudolf Steiner, the founder of anthroposophy and anthroposophical medicine. Since the 1980s, mistletoe therapy has been researched systematically. A number of German phyto-pharmacological providers like WELEDA, ABNOBA HEILMITTEL, HELIXOR HEILMITTEL, NOVIPHARM and MADAUS market a range of different misteltoe preparations. Some products, e.g. those from WELEDA are anthroposophical, i.e. fermented and diluted preparations, others are herbal extracts. Indications within the anthroposophical approach depend on the host tree of the misteltoe plant.

Description of treatment method

Mistletoe is usually injected subcutaneously, but other routes of administration (e.g. intravenous, peritumoural, or intrapleural) also exist. The dosing regimens vary according to extract type and either follow a constant or a variable dose.

Claims of efficacy / mechanisms of action / alleged indication

Proponents claim that mistletoe treatment improves quality of life, strengthens the immune system and enhances cancer remission and survival rates. These actions are thought to be caused by lectin which are believed to induce macrophage cytotoxology, stimulate phagocytosis and increase cytokine secretion.

Prevalence of use

Mistletoe is popular in continental Europe, particularly in Germany. A recent study for Germany, for instance, showed that 15% of lung cancer patients used misteltoe preparations, most in order to "support the tumor treatment". 4 For other cancers, the prevalence figures may be even higher. The prevalence of usage shows important national differences.

Legal issues

In Germany, Switzerland and Austria, mistletoe preparations are licensed medicines that are partly reimbursable through the official healthcare system. In other European countries, they have no license. In the United States, Iscador is the only mistletoe product approved for distribution by the FDA in accordance with its requirements for homeopathic medicines. At present, at least two U.S. investigators have IND approval to study misteltoe as a treatment for cancer. 5-6 The FDA has not approved the use of mistletoe as a cancer treatment.

The Medicines and Healthcare Regulatory Agency in the UK states that, if a company places a

manufactured herbal remedy on the market and supplies the product to herbalists, then such a product would need to have either a marketing authorisation or traditional use registration (http://www.mhra.gov.uk/). This is in accordance with the European Directives and Regulation of herbs.

Costs and expenditures

The costs of extracts varies. In Germany, a course of treatment lasting 2-3 weeks would typically cost around 40 Euros.

Does it work ?

Pre-clinical studies

Misteltoe extracts have been shown, in various test models, to stimulate the immune system. 7-11 Animal studies have demonstrated that mistletoe extract increases DNA stability, 12 and inhibit cell growth. 13-14 Antitumour activity of *Viscum album* L. extracts has been reported from animal experiments. 10,15 It has also been suggested that mistletoe may be beneficial in decreasing the adverse effects of chemo- and radiotherapy and that it may counteract the effects of drugs used to suppress the immune system. 16-18

Uncontrolled trials

There are numerous uncontrolled clinical studies, which suggest anti-cancer effects of mistletoe. 19 Their results are open to bias and therefore less conclusive than those from controlled clinical trials. 20

Controlled trials and systematic reviews

Numerous reviews are available and their conclusions are somewhat contradictory. e.g.19,21-27 Observational and retrospective controlled clinical trials tend to generate encouraging results. e.g.22-23 A striking finding is the phenomenon that reports by investigators with affiliation to anthroposophical institutions invariably arrive at positive conclusions.

A Cochrane review (such assessments' tend to be scrupulously independent and transparent) aimed at determining the effectiveness, tolerability and safety of misteltoe extracts either as a monotherapy or administered as an adjunct to conventional cancer treatment. 24 The outcome measures considered included survival times, tumor response, quality of life (QoL), psychological distress, adverse effects of cancer therapies and safety of mistletoe extracts. Twenty-one randomised clinical trials (RCTs) met all the inclusion criteria. Thirteen of these studies investigated survival, and 6 of them showed some evidence of a benefit but none were of high methodological quality. Sixteen RCTs investigated QoL, psychological distress, performance index, symptom scales or adverse effects of chemotherapy. Fourteen of these studies showed some evidence of a benefit, but only two were of high methodological quality. The authors

concluded that “the evidence from RCTs to support the view that the application of mistletoe extracts has impact on survival or leads to an improved ability to fight cancer or to withstand anticancer treatment is weak”. 24

A similar, but more recent systematic review, included 18 RCTs. 25 It confirmed the insufficient evidence in terms of life expectancy, but indicated positive effects on quality of life. The authors concluded, however, that the quality of the primary studies was "mostly low". Finally, these authors, were unable to identify marked differences between various preparations and advocate the use of the umbrella term "misteltoe therapy" for all of them.

More recently, Ostermann et al. evaluated 49 Iscador® studies with different designs. 26 They found relatively clear effects in favour of Iscador versus no treatment of survival. But there was evidence of publication bias and, focussing on just randomised studies, the effect was no longer significant.

Braedel-Ruoff specifically evaluated studies testing the effects of Iscador on natural killer cell activity. 27 She found that many of these trials demonstrated a positive effect. However, the evidence was not complelling and the author felt that more investigations were necessary to be sure.

Is it safe ?

The above-mentioned Cochrane review showed that mistletoe extracts are usually well tolerated and cause few adverse effects. 24

Contraindications, precautions, warnings

Avoid using mistletoe during pregnancy and whilst lactating as mistletoe has uterine stimulant activity.

Adverse effects

In large dosages, mistletoe extracts can cause significant toxicity and can lead to vomiting, diarrhoea, intestinal cramps, hepatitis, hypotension, seizures, and contraction of the pupils. Subcutaneously, mistletoe can cause pain and irritation at the injection site, chills, fever, headaches, angina and allergic reactions, which sometimes can be severe. There is usually some local inflammation at injection site and an increase in body temperature which may be accompanied by headaches and chills. 28 It is also suggested that ingestion of the plant or intravenous administration of some of the plant constituents may cause seizures, bradycardia and death. 28 One case of a possible association between a patient treated with a combination herbal product (one of the ingredients was mistletoe) and hepatitis was reported. 29

Interactions

There is some evidence that European mistletoe might interact with hawthorn, as it might decrease its effectiveness due to its cardiotoxic and negative inotropic effects 30 and might thus cause hypotension or decrease the effectiveness of immunosuppressant.

Quality issues

Several different mistletoe extracts exist on the market. They all comply with the accepted quality standards. Anthroposophical preparations are usually based on fermented extracts, while herbal extracts are not.

Citation

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