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Introduction

Through great advances in medical research over the course of the last decades, many types of cancer have become curable. However, a cancer diagnosis will still come as a shock to the ones affected, and to their loved ones.

Established so-called «conventional» treatments for cancer include surgery, chemotherapy, radiotherapy, hormone therapy and immunotherapy. The majority of patients also use complementary treatments to support themselves throughout their journey. In Switzerland, mistletoe therapy, which supports the body's regulative capacities and immune functions, is the most commonly prescribed complementary therapy.

History of mistletoe therapy

The Celts revered mistletoe as the «all-healing» plant. In the Middle Ages, its extract was used to treat liver problems and to lower blood pressure. At the beginning of the 20th century, there was a renewed interest in this special plant. Around 1907, botanist Karl von Tubeuf from Munich assembled all the scientific, mythological and cultural knowledge about mistletoe available at the time. In 1923, he published this collection in a volume entitled «Monography of Mistletoe». Dr Rudolf Steiner, the founder of Anthroposophy, had already started to lecture on mistletoe in the autumn of 1904 as part of his teaching and research activities in the humanities.

His ideas were taken up by the Dutch physician Dr Ita Wegman who, together with a Swiss pharmacist, developed the first mistletoe preparation for injection with the aim to strengthen and support her cancer patients. As early as 1917, she used it in her practice in Zurich to treat patients with promising results. By 1920, the knowledge of mistletoe therapy was established well enough to justify its presentation at the first anthroposophical course for doctors in Dornach, Switzerland. In 1935, Dr Ita Wegman founded the Society for Cancer Research (VfK) together with her colleagues in Arlesheim, Switzerland. Up to the present day, the society's mission includes research into mistletoe therapy.

In Europe, mistletoe preparations are among the most commonly prescribed supportive remedies for cancer patients. Mistletoe is one of the best-researched medicinal plants. The main aim of mistletoe therapy is to improve the patient's quality of life. During mistletoe therapy, many patients experience an improvement in general well-being, normalisation of sleep patterns, and a restoration of appetite and vitality.

Mistletoe therapy may relieve tumour-related pain, strengthen the immune system and alleviate side effects of conventional therapies.

Mistletoe botany

Some of the myths surrounding mistletoe can be explained by its botanical properties. Mistletoe is a very peculiar plant indeed. It does not take root in the ground, but needs trees and shrubs to grow on. The white, translucent berries do not contain seeds, but usually two tiny pre-formed green plants («embryos») which, unlike «normal' plant seeds, would perish in darkness. Bird species such as mistletoe thrushes and waxwings eat the berries and excrete the seeds, which will often stick to the branches of trees and shrubs they happen to fall on. The blackcap will only eat the skin and pulp of the berries and stick the mistletoe embryos directly onto the branch on which it is perching. The mistletoe embryos form sinkers that anchor themselves to the tree, providing the germinating mistletoe with water and nutrients. Very slowly, the mistletoe bush develops its typical spherical shape. Mistletoe does not begin to flower before having reached five to seven years of age. When it is 10 to 15 years old, it can be harvested and processed into a pharmaceutical product.

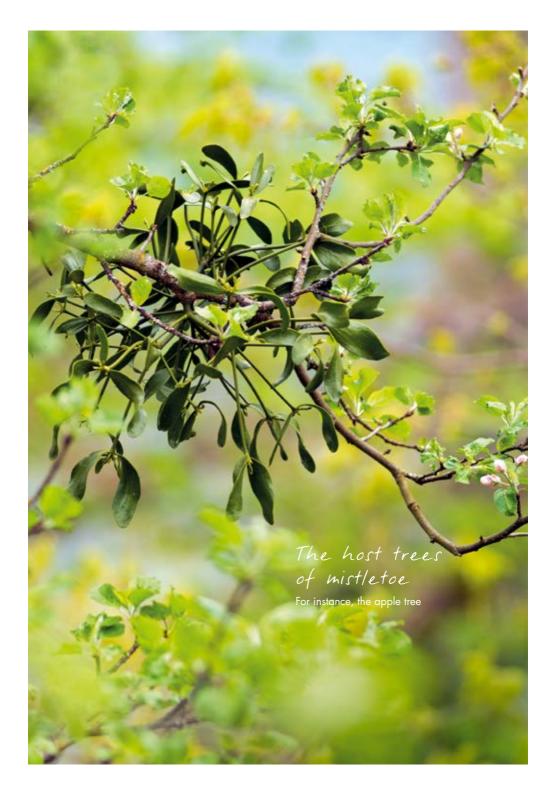
Only white berried mistletoe (*Viscum album* L.) is used for application in cancer. In Central Europe, it occurs in three subspecies, namely deciduous mistletoe, pine mistletoe and fir mistletoe.

The deciduous tree mistletoe occurs particularly frequently on apple trees and poplars, but is also found on maples, birches, lime trees, almond trees, robinia, willows, hawthorns, but only rarely on oaks and elms.









Active ingredients and their effects

Mistletoe extracts are known to act in many different ways. They can stimulate the immune system and, in the lab, have been shown to damage tumour cells. They can also stimulate healthy cells to better protect their genetic material from damage. Mistletoe therapy may reduce the side effects of conventional oncological therapies without impairing their effectiveness, thus improving the patient's quality of life. Tumour-related fatigue may also be reduced significantly. The frequently observed improvement in well-being and reduction in pain caused by mistletoe extracts is attributed to an increased release of the body's own beta-endorphins.

The observed effects are based on several different substances. Mistletoe extracts contain a large number of medically interesting compounds, of which mistletoe lectins and viscotoxins are among the best-researched.

The levels of the different compounds of mistletoe vary depending on the season, the stage of development of the plant, the time of harvest, the location and the host tree on which it grows.

Experiments in the lab have shown that mistletoe lectins can inhibit the growth of cancer cells, or even kill them. Mistletoe lectins also have an immunomodulatory effect. There are three different types, called mistletoe lectin I, II and III. Each of these mistletoe lectins can potentially induce the death of cancer cells. Programmed cell death or «apoptosis» is a natural occurrence in the body as the organism is constantly producing new cells to replace old and possibly impaired ones. Cancer cells, however, have lost the ability for apoptosis and thus multiply out of control. Stimulating or restoring the ability of cancer cells for programmed cell death would help to limit the growth of cancer cells.

Viscotoxins are small protein molecules. In experiments, they were able to dissolve cancer cells by destroying their cell membranes (cytolytic effect, necrosis). Like lectins, they can also stimulate the immune system. In particular, they increase the efficacy of natural killer cells and granulocytes, subgroups of white blood cells that are active against viruses and bacteria, but also against cancer cells. As mistletoe lectins are abundant in the plant during winter while viscotoxins are only found in summer, mistletoe is harvested twice a year, in June and December. The extracts from the summer and winter mistletoe are then blended in a special machine. This manufacturing process ensures that the preparation contains the widest possible range of the valuable



substances mistletoe produces over the course of the year and makes them available to support cancer treatment. Mistletoe therapy has an immunomodulatory effect, i.e. it activates cells of the immune system, improving the body's defences. This can be useful in cancer therapy in three ways:

- The immune system becomes more efficient at recognising cancer cells, thereby counteracting the tumour's tendency towards metastasis.
- Standard therapies such as surgery, radiotherapy, chemotherapy, (anti)-hormone
 therapy or immunotherapy challenge the body. If the immune system and the
 function of healthy cells is supported by mistletoe therapy, it can, for instance,
 better fight infectious diseases, and patients may recover more quickly.
- An intact immune system also helps to prevent relapses following remission.
 Mistletoe therapy should therefore be continued for a certain time even after the successful conclusion of conventional oncological treatments.

Holistic effects

Many cancer patients tend to feel cold because the disease negatively impacts their ability to regulate their body temperature. In this situation, mistletoe therapy is experienced as having a warming effect and normalising body temperature. Mistletoe therapy may enable patients to newly establish a relationship with their body by recognising and understanding its signals and to better care for themselves. This is particularly important during the recovery period after surgery, and also when the body is affected by the side effects of conventional oncological treatments.

It's often been observed that mistletoe therapy has an energizing effect, awakening the spirit and alleviating anxiety. In addition to supporting quality of life, mistletoe therapy can empower patients to find strength and meaning on their personal journey.



Administration

Mistletoe extract is administered by subcutaneous injection, i.e. into the tissue under the skin, in the same way as insulin or heparin injections, and patients may do it themselves. At least the first injection should be carried out under the supervision of a healthcare professional. Mistletoe extract is usually injected two to three times a week. Due to its energising properties, the injection may best be done in the morning, although no negative effects are to be feared if it is applied later in the day.

What to keep in mind when applying mistletoe extracts

Mistletoe preparations should ideally be kept in the refrigerator. Immediately before injection, the ampoule may be briefly warmed in one's hands. Preferred areas for subcutaneous injections are the abdominal area and the outer side of the thigh. Injection is performed into a skin fold at an angle of 30°-45° to the skin surface, just below the skin.

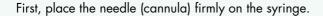
Redness around the injection site (up to a maximum of 5 cm in diameter), with localized swelling and itching, may occur temporarily and indicates a positive reaction of the immune system to the mistletoe extract. The reaction will usually subside within a few days. The next injection should only be given after the reaction to the previous one has disappeared. The injection site should be changed regularly to allow the skin to recover. Care should also be taken not to inject into areas of inflamed or injured skin, or into sites where surgery or radiotherapy have been, or are planned to be, performed.



Have a look at our self-injection video tutorial: www.iscador.com/injection

For each injection you will need the following items:

- an ampoule of mistletoe extract
- a small syringe (2 ml)
- a short, thin needle
 (e.g. 0.4 x 19 mm, No. 20 or 27G)
- an alcohol swab
- a dry swab (optionally)
- a small band-aid (optionally)



Hold the ampoule carefully between the thumb and the index finger with the coloured dot on the ampoule neck facing towards you. Remove the liquid from the top of the ampoule by gently tapping it, and then open the ampoule. First, place a simple dry swab around the head of the ampoule to protect your fingers. Holding the ampoule head with the coloured dot facing towards you, gently bend the head of the ampoule backwards with light pressure. It will break around a designated area enabling you to carefully draw up the liquid into the syringe through the needle. When you carry out your first injection, your healthcare professional will be able to guide you how to do it safely and securely.





Having drawn up the liquid from the ampoule into the syringe, next remove the excess air from the syringe. To do this, hold the syringe vertically with the needle pointing upwards. By gently tapping the syringe, small air bubbles contained in the liquid will float upwards. Gently push the plunger upwards. A small drop of liquid appearing at the tip of the needle is an indication that the syringe and needle have been emptied of air and are now filled with liquid.

Your healthcare professional will then show you how to safely apply the injection yourself:

- Generously disinfect the injection site and the area around it with an alcohol swab; leave to dry for at least a minute.
- Take a fold of abdominal skin between your thumb and index finger.
- Inhale, then while exhaling, quickly insert the needle at an angle of 30° to 45° to the surface of the skin at a depth of 3–5 mm.
- Slowly and evenly inject the contents of the syringe.

Ampoule opening

- Hold the alcohol swab to the injection site and pull the needle out of the skin.
- Press the swab firmly against the injection site for a few seconds. If necessary, the injection site can be covered with a small band-aid.

Subcutaneous injection (under the skin)

Drawing up the injection liquid

Reactions

Following the injection, body temperature may rise up to 38° C, but will return to normal within 24 hours. This reflects an activation of the immune system, which is a desired effect of mistletoe therapy.

From 6–12 hours following injection, a slight reddening of the skin around the injection site may appear. This is known as the «local reaction». It may be accompanied by itching, swelling, and warmth in the area. The local reaction may be used to determine the best individual dose and indicates the body's response to the mistletoe proteins. It should not exceed 5 cm in diameter as this may cause unnecessary discomfort. The local reaction usually disappears spontaneously after 1–2 days. As the duration of treatment increases, it may diminish or disappear altogether. However, this does not mean that the effect is not sustained.



Typical image of a local reaction

Frequently asked questions

What is the role of mistletoe in integrative oncology?

Mistletoe therapy is an essential component of a holistic, i.e. integrative, cancer treatment. Many national and international clinical guidelines recommend it to complement guideline-based oncological therapies like surgery, chemotherapy, radiotherapy, (anti)-hormone therapy and/or immunotherapy. The main aim of this complementary therapy is to improve the patient's quality of life.

For how long has mistletoe therapy been around?

Mistletoe preparations have been used in the treatment of cancer patients for more than 100 years. Today, they are among the most frequently prescribed complementary remedies in the German-speaking countries.

Has mistletoe therapy been scientifically proven?

Preclinical trials exploring the pharmaceutical properties of mistletoe, including animal studies, were first conducted in the first half of the 20th century. To this date, a number of mistletoe's molecular working mechanisms have been established. There are more than 160 clinical trials on the use of mistletoe preparations in different types of tumours. Mistletoe preparations rank among the best and most extensively studied drugs in supportive cancer treatment. The majority of clinical trials has shown a benefit for mistletoe therapy. The most consistent evidence exists on the reduction of side effects of conventional therapies and the improvement of quality of life. As a result, sometimes an increase in survival rate has been documented.

What are the active ingredients in mistletoe?

Mistletoe contains a large number of active ingredients. Some of these, such as mistletoe lectins and viscotoxins, have well-documented effects useful during cancer treatment. However, whole plant mistletoe extracts are still used over single substance drugs because the naturally occurring constituents in mistletoe complement each other in a meaningful way.

What are the effects of mistletoe therapy?

Mistletoe therapy may improve general health and quality of life. This may become evident, for example, in a normalisation of appetite and body weight, an improved quality of sleep, a sensation of warmth and well-being, and a mental stabilisation. There may be an improvement in mood, an increase in resilience and in initiative.

Tumour-related pain may also be reduced. Recent study results suggest that under certain circumstances, mistletoe therapy may prolong survival. In lab experiments, mistletoe preparations were able to inhibit the growth of malignant cells without affecting healthy tissue. Mistletoe extracts stimulate the body's immune system.

What is the effect of mistletoe therapy on surgery, on chemotherapy, or on radiotherapy?

As mistletoe therapy has an immunomodulating effect, mistletoe extract taken up to 14 days before an operation can improve recovery and thus the postoperative course. After successful tumour removal surgery, mistletoe therapy can help to prevent relapses.

Mistletoe therapy can be used to supplement or support chemotherapy/radiotherapy as it reduces their side effects and improves the tolerability of these therapies without impairing their efficacy.

However, mistletoe injections must not be applied in or near to operation or radiation sites as the skin at these sites needs to be protected from injury and inflammation.

What is the benefit of having mistletoe preparations from different host trees?

The constituents of mistletoe differ depending on the respective type of host tree. For this reason, mistletoe therapy may be personalized to achieve the best possible treatment outcome by choosing a preparation in accordance with the type of tumour and the patient's constitution.

Are there differences between mistletoe products from different manufacturers?

Although all manufacturers utilize mistletoe as the base material for their preparations, they employ different methods of extraction. Consequentially, mistletoe preparations from different manufacturers differ in composition, even though the mistletoe may come from the same type of host tree. When switching from one manufacturer's preparation to another, the manufacturer should be contacted for advice which host tree should be prescribed as a follow-up treatment to the previous prescription, and treatment should be re-initialized from the lowest available dose.

How are mistletoe preparations administered?

Mistletoe preparations are administered by injection under the skin (subcutaneously), similar to insulin injections. Following an instruction by a healthcare professional, this can be done by the patients themselves.

Is there an ideal time to start the treatment?

Depending on the therapeutic setting and the respective treatment objectives, mistletoe preparations may theoretically be administered at any point in a treatment programme and at any stage of the disease. In principle, treatment should be started as early as possible, but ultimately the point of commencing may be decided individually upon by the patient and their treating physician.

How often should I inject mistletoe preparations?

Mistletoe preparations are usually injected two to three times a week according to an individualized protocol determined by the patient's response to the treatment. Especially in the first two to three years of treatment, an injection frequency of three times a week (e.g. Monday, Wednesday, Friday) is recommended.

How do I know if a dose works?

Mistletoe extracts are administered in increasing dosage. Having reached a certain dosage, a reddening of the skin will occur, possibly in combination with a localized itching, swelling and/or warming around the injection site. Ideally, this local reaction will not exceed a maximum diameter of 5 cm around the injection site, as it will cause unnecessary discomfort otherwise. Also, a general increase in body temperature up to 38° C may occur, but should not exceed this temperature for the same reason. Generally, even before this type of reaction is achieved, there may be a gradual improvement in general condition with a positive effect on appetite and weight, normalisation of sleep, a feeling of warmth and resilience, a reduced susceptibility to infection, an increase in initiative and confidence, self-regulation and motivation. It is possible for local reactions to diminish or disappear over the course of a long-term treatment without the efficacy of mistletoe therapy being impaired.

Are there any side effects? If so, what are they?

Although mistletoe therapy is generally well tolerated when used as directed, and significant adverse effects are rare, side effects may occur as with every treatment. Local reactions of more than 5 cm in diameter may indicate the administered dosage having been too high. In this case, the treatment should only be continued after the symptoms have subsided, and initially at a reduced dose (e.g. going back to the next lower concentration, or applying only half an ampoule). The same goes for generalised reactions such as a rise in body temperature above 38° C, or flu-like symptoms following injection. These need to be further investigated and evaluated. As with

every medication, allergic reactions may occur and would warrant immediate medical attention, followed by a discontinuation of treatment.

How can I tell the difference between local reactions and side effects?

A temporary reddening and possibly itching at the injection site, together with a slight increase in body temperature, are desirable and expected responses to mistletoe therapy. Local reactions at the injection site up to a maximum of 5 cm in diameter and a temperature rise of up to 38° C are considered «normal». However, if reactions are more pronounced or if a patient cannot tolerate them, they constitute side effects. Side effects should be reported to the manufacturer and lead to a modification of the treatment regimen.

Does mistletoe interfere with other therapies or medications?

There are no known negative interactions between mistletoe extracts and other treatments. Mistletoe can be used alongside chemotherapy, radiotherapy, (anti)-hormone therapy or immunotherapy.

How long should mistletoe therapy be continued?

Mistletoe therapy may be continued alongside any conventional oncological treatment and beyond, depending on the risk of recurrence. In most cases, this means that therapy should be continued for about five years, ideally from the time of the diagnosis.

How should mistletoe preparations be stored?

To conserve the quality of compounds contained in herbal products, mistletoe extracts should be stored in the refrigerator at 2 to 8° C over longer periods of time (e.g. if stored at pharmaceutical wholesale retailers and pharmacies). Temperatures of up to 30° C may be tolerated for short periods during transport (from the pharmacy to your home or while travelling) without negatively affecting the remedy. However, the ampoules should not be left in the sun or near a heater.

Useful addresses and links

Camphill Wellbeing Trust

St. Devenicks, Murtle Estate, Bieldside Aberdeen AB15 9EP United Kingdom www.camphillwellbeing.org.uk

National Centre for Integrative Medicine

Chapel Pill Lane, Pill Bristol BS20 OHH United Kingdom ncim.org.uk

NHS Centre for Integrative Care

Gartnavel Hospital
1053 Great Western Road
Glasgow G12 ONR
United Kingdom
https://www.nhsggc.scot/hospitals-services/
main-hospitals/gartnavel-general-hospital/
nhs-centre-for-integrative-care/

Friends of NHS Centre for Integrative Care

1053 Great Western Rd Glasgow G12 0YN United Kingdom friendscic.org

Penny Brohn UK

Ham Green House, Chapel Pill Lane, Pill Bristol BS20 OHH United Kingdom pennybrohn.org.uk

Physicians Association for Anthroposophic Medicine (PAAM)

PO Box 880 Moab, UT 84532 United States of America anthroposophicmedicine.org

Royal London Hospital for Integrated Medicine

60 Great Ormond Street London WC1N 3HR United Kingdom www.uclh.nhs.uk

St Luke's Therapy Centre

53 Cainscross Rd Stroud GL5 4EX United Kingdom www.stlukestherapycentre.co.uk

Synthesis Clinic

Castle End Business Park 6, Castle End Rd Reading RG10 9XQ United Kingdom www.synthesisclinic.co.uk

Yes to Life

Integrative Cancer Care Charity 71-75 Shelton Street Covent Garden London WC2H 9JQ United Kingdom yestolife.org.uk

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Impressum

«Mistletoe therapy for cancer»

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Please take note of the patient information enclosed with ISCADOR. Should you have any further questions or require further information, please contact your healthcare professional.

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