

ANALYSIS OF THE POTENTIAL OF VISCUM ALBUM IN THE ANTICANCER PERSPECTIVE OF COMPLEMENTARY MEDICINE

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Abstract: Cancer is a growing threat to global health, with conventional treatments often associated with severe adverse side effects. Complementary therapy with *Viscum album* (mistletoe) is highlighted due to its therapeutic properties, including immunomodulation and antitumor effects. This study evaluates the impact of mistletoe as a complement in cancer treatment, focusing on improving quality of life, reducing side effects and the potential impact on tumor regression, in addition to preventing relapses, highlighting the need for additional clinical studies to validate its efficiency. This literature review examined 19 articles and one clinical case from the last 10 years across multiple databases, providing valuable insights into the therapeutic use of mistletoe in cancer treatment. *Viscum album* has components such as viscotoxins and lectins, which exhibit anticancer activity, promoting apoptosis and stimulating the immune system. Several studies indicate improvements in quality of life and immunological responses with the use of mistletoe, therefore, mistletoe is a promising complementary therapy that, when integrated with conventional treatments, improves the quality of life of cancer patients, despite the need for additional research to understand its mechanisms of action and effectiveness in different types of cancer.

Keywords: *Viscum album*. Cancer. Complementary therapy. Neoplasms.

INTRODUCTION

Cancer represents a significant global public health challenge, with an increase of approximately 20% in the incidence rate over the last ten years. Projections indicate that in 2030, significant growth is expected, with more than 25 million new cases worldwide (SANTOS et al., 2023).

Conventional treatments (CTs), such as chemotherapy and/or radiotherapy, impose

obstacles on the patient. The side effects and immunosuppression associated with these CTs negatively affect patients' quality of life. Given this reality, the use of complementary and integrative approaches to deal with adverse effects has grown in relevance. Among these alternatives, therapy with *Viscum album* L. (VA), known as mistletoe, emerges as one of the most popular options adopted by cancer patients in Europe as a complement to CTs (OEI et al., 2019a). This approach seeks to harness the potential benefits of mistletoe, including improved quality of life, increased survival and greater tolerance to oncological therapies. This is due to the therapeutic properties of VA, which encompass immunomodulation, cytotoxicity and induction of tumor apoptosis, followed by an intense immunological reaction, among other benefits (MÜNST et al., 2013).

Mistletoe is a medicinal plant known for being rich in bioactive components. Viscotoxins and lectins, present in its aqueous extracts, stand out as the main active substances. Pre-clinical and clinical investigations have suggested that VA preparations may have antitumor (MARVIBAIGI et al., 2014), immunomodulatory (WROTEK et al., 2014), anti-inflammatory (NICOLETTI, 2023) and antioxidant (NAZARUK) effects; ORLIKOWSKI, 2016). In addition to viscotoxins and lectins, the presence of smaller molecules is also notable, such as phenolic acids, flavonoids, terpenoids, tannins, phytosterols, saponins and organic acids, which possibly contribute to their biological properties (PEÑALOZA et al., 2020). And studies report that VA therapy can improve the quality of life of cancer patients by reducing fatigue, improving sleep, and reducing anxiety and depression, and VA therapy is reported to be generally well tolerated (OEI et al, 2020; MÜNST et al., 2013) with a low incidence of severe side effects and can be commonly

combined with CTs (MARVIBAIGI et al., 2014).

Given the studies analyzed, the following question arises: how can VA be used as a complementary therapy in cancer treatment? Experimental and clinical research has indicated that preparations of this extract have the mechanism of inhibiting angiogenesis and angiogenic factors, proving to be a crucial therapeutic strategy for the treatment of cancer, and mistletoe extracts have demonstrated antiangiogenic effects (STEELE et al., 2015). And other studies have also examined the hypothesis that VA preparations induce the activation of human dendritic cells that facilitate effective tumor regression and can inhibit tumor growth, induce cancer cell apoptosis, modulate the immune response and reduce angiogenesis (STEINBORN et al., 2017).

Mistletoe has shown its therapeutic potential in cancer treatment and based on the data obtained, the purpose of this study is to analyze the impact of using VA as a complementary therapy in cancer treatment. In which bibliographic investigations and analyzes of clinical and pre-clinical studies related to the topic will be conducted. However, it is necessary to develop more clinical studies that can prove its efficacy and therapeutic potential.

METHODOLOGY

This descriptive study adopts a literature review approach that aims to evaluate the use of mistletoe in complementary therapy for cancer, considered a highly complex pathology. To achieve this objective, 19 articles and one clinical case were analyzed, obtained through databases such as Scielo, Pubmed, VHL Brasil, Revista Brasileira de Cancerologia and Revista arte Médica amplidad. The descriptors used were “*Viscum Album*”, “Mistletoe”, “Neoplasias malignans”, “Quality

of life”, which met the criteria established for inclusion. To be considered, studies needed to have been published in the last 10 years and be available in English, Portuguese or German, in addition to being related to the objective of the review and demonstrating methodological quality. An exception was made for the article by author Magano, (2012), due to its relevance to the study. A detailed and precise analysis of the data from the 19 articles and the clinical case was carried out, being collected and organized in a systematic way. Initially, the articles were read in full, in which relevant data were extracted and grouped by categories, such as “use of mistletoe in complementary oncological therapy”, “side effects”, “improvement in quality of life”. Subsequently, an in-depth review was carried out on the data collected to determine patterns and discrepancies in information. A quantitative analysis of the information obtained was also carried out, with the aim of identifying the frequency of certain points and results in the articles obtained. The conclusions arising from the aforementioned processes were used strategically to prepare this study. This literature review represents a significant effort to collect and explore important data on the therapeutic efficacy of mistletoe in the complementary therapy of neoplasms, playing a fundamental role in advancing understanding in this area.

DEVELOPMENT

ONCOLOGY: EXPLORING COMPLEMENTARY THERAPIES

In the current medical scenario, cancer represents a growing threat to the increase in life expectancy, showing a rapid increase in the incidence of mortality (SANTOS et al., 2023). Given this reality, it is essential to understand that human cancer has its roots in a complex molecular basis, involving several genes in

the process of carcinogenesis. Among these genes, proto-oncogenes stand out, which play a fundamental role in the regulation of various processes. Proto-oncogenes are responsible for controlling growth factors, cellular signal transduction and nuclear transcription factors. It is important to highlight that these genes play a crucial role in the emergence of tumors. Oncogenes, in turn, act in synergy with the aim of promoting malignant transformations (KONTOMANOLIS et al., 2020).

It is important to highlight that, from a pathological point of view, cancer presents specific characteristics. This includes abnormal signal transduction, which results in uncontrolled cell multiplication, the ability to metastasize, the loss of the apoptosis process and the induction of angiogenesis, which culminates in the emergence of neoplasms (KONTOMANOLIS et al., 2020). Faced with this reality, cancer patients face the challenge of living with cancer, which is why integrative and complementary medicine plays a significant role.

A notable example is the use of anthroposophic medicine, in which Rudolf Steiner, the creator of this approach, introduced the use of mistletoe extract in oncology as an unconventional way of treating cancer in 1920. This is due to the high therapeutic potential of the extracts of mistletoe in the treatment of cancer. Therefore, this anthroposophic medicine, which is a herbal drug, becomes relevant, especially due to the minimal side effects and the absence of risks to life associated with its use (MARVIBAIGI et al., 2014).

In oncology, mistletoe therapy stands out significantly and is widely used in the treatment of cancer. Due to its remarkable therapeutic potential, it has become imperative to conduct more clinical trials with the aim of evaluating its efficacy, its relationship with tumor control, increasing survival and improving patients'

quality of life. Furthermore, it is important to investigate the possible side effects that this therapy could cause compared to conventional therapies (KIENLE; KIENE, 2017).

VISCUM ALBUM: THE SPECIAL PLANT

Mistletoe is considered a special plant, it was once considered a panacea due to its beneficial properties. However, some time ago, part of the plant, specifically the berries, was questioned and considered to be poisonous and pose health risks. This cast doubt on its medicinal use. However, more recently in the previous decade, medicinal interest in mistletoe has resurfaced due to its selective action on tumor cells. Therefore, this phytomedicinal substance has gained ground in central Europe, where the use of hydroalcoholic extracts from European mistletoe has been widely consumed. Mistletoe can be present in diets, homeopathy, herbal medicine and even veterinary medicine. However, its greatest use is in adjuvant therapy against cancer, due to the positive effects on the patient's quality of life and immune system (NICOLETTI, 2023).

OViscum album L., also known as European mistletoe, is a hemiparasitic shrub from the Viscaceae family (Loranthaceae) as can be seen in Figure 1. Mistletoe is used as a pharmacognostic medicine, in herbaceous presentation, that is, they are viscous herbs. Around 1500 species of mistletoe have been identified, which are located in different regions. Among the mistletoes belonging to the Viscaceae family, *Viscum album L* (European mistletoe), *Phoradendron serotina* (American mistletoe), *Phoradendron leucarpum* (Mexican mistletoe) and *Phoradendron juniperinum* (juniper mistletoe) stand out. Belonging to the Loranthaceae family, we have *Dendrophthoe pentandra* (Indonesian mistletoe), *Viscum coloratum* (Korean mistletoe), *Dendrophthoe*

falcata (Indian mistletoe) and *Loranthus tanakae* (Chinese mistletoe). Despite all these mistletoe species, the genus that has been widely studied and scientifically explored is *Viscum album* L., of European origin. In the pharmaceutical industry, we find mistletoe with trade names such as Isorel, Eurixor, Iscador, Helixor, Cefaleksin, Lektinol, Iscucin and Abnobaviscum. These preparations are injectable and can only be purchased with a medical prescription (NAZARUK; ORLIKOWSKI, 2016).



Figure 1. Infestation of *Viscum album* subsp. *album* L. on a *Populus* sp. host tree, side view by drone.

Source: Wikimedia Commons (2006)

VISCUM ALBUM: UNDERSTAND THE ANTI-CANCER OF ANTHROPOSOPHY

The *Viscum album* L. preparations, discussed by Rudolf Steiner, highlight that their indications for the treatment of cancer are supported by the type of host tree. Each host tree, according to Steiner, has a specific effect on the medicine. Therefore, Steiner emphasizes that the relationship between mistletoe and the host tree is essential. He quotes: “The *Viscum* takes as an external substance what is the etheric hypertrophied in cancer and thereby strengthens, by the fact that it rejects the physical substance, the effect of the astral body and thus leads the cancer tumor to collapse, to disintegrate” (KALIKS, 2017).

Viscum album L. preparations, as discussed by Rudolf Steiner, highlight that their indications for the treatment of cancer are related to the type of host tree. There are three subspecies: *Abietis* (*abieto*), *Mali* (*apple*) and *Pini* (*pine*). The *abietis* subspecies specifically parasitizes specimens of the genus *Abies* (*fir trees*); the *austriacum* subspecies also specifically parasitizes specimens of the genus *Pinus* (*pine trees*), and the *album* subspecies parasitizes other deciduous trees. The choice of the type of mistletoe to be used is determined by the patient’s pathological characteristics (MÜNST et al., 2013; MAGANO, 2012).

For a more comprehensive understanding of *Viscum album* L., it is important to understand its chemical composition. Studies report that several types of metabolites were isolated from mistletoe, being of great relevance for botanical, phenomenological, phytochemical, pre-clinical and clinical studies (NAZARUK; ORLIKOWSKI, 2015; MAGANO, 2012; KALIKS, 2017; NICOLETTI, 2023; OEI et al., 2019a; OSTERMANN et al., 2020; OEI et al., 2020; OEI et al., 2019b; ROSTOCK, 2020; STEELE et al., 2015; LOEF; WALACH., 2020). It is worth noting that many of these metabolites are not produced by the plant, but by the host tree (NAZARUK; ORLIKOWSKI, 2016). In *Viscum album* L. extracts, we find components of greater importance, such as viscotoxins and lectins, which have high molecular weight (PEÑALOZA et al., 2020).

Within *Viscum album* L., there are components of great biological relevance. Viscotoxins, for example, are polypeptides with cytotoxic activities that induce cell membrane lysis and apoptosis, thus protecting DNA. Furthermore, they act as immune system stimulators (MAGANO, 2012). Viscotoxins are capable of promoting cell death through necrosis (KIENLE; KIENE., 2017). Among the viscotoxin isoforms, the most reported and predominant are A1, A2, A3 and B,

with viscotoxin A3 being an especially active isoform, with comparative membrane interactions (NICOLETTI, 2023).

Another component of great relevance in mistletoe are lectins, also called viscolectins, which are active in inducing cell apoptosis (KIENLE; KIENE., 2017). Viscolectins are glycoproteins with binding affinity to sugars in membrane cells (NICOLETTI, 2023), and are considered most responsible for the antitumor activity of *Viscum Album*, including viscolectin I, viscolectin II and viscolectin III. These lectins have the ability to stimulate the immune system, limit protein synthesis in ribosomes and induce apoptosis, that is, the programmed death of cells (MAGANO, 2012).

With the understanding of viscotoxins and viscolectins, which play a great role against cancer cells due to their cytotoxic, apoptotic and immunomodulatory effects, it is necessary to emphasize that mistletoe includes other essential components in its composition for anthroposophic medicine (ROSTOCK, 2020). Within the constituents of mistletoe there are active biological compounds such as: monosaccharide and polysaccharide carbohydrates; fats; amino acids; oligosaccharides; enzymes, flavonoids, glycoproteins (lectin MLT), triterpenic acids, polypeptides (viscotoxin), vesicles; triterpene acids such as oleanolic and betulinic acids (MÜNSTER et al., 2013; MARVIBAIGI et al., 2014). It must be noted that the chemical components of mistletoe can be affected by variations due to extract preparation techniques, among other external factors such as the season and harvest time, the commercial producer and growth stages influence (MARVIBAIGI et al., 2014).

VISCOTHERAPY: TREATMENT FOR CANCER PATIENTS

As previously mentioned, mistletoe demonstrates immunomodulatory activities that have the power to influence immune responses, both in vitro and in vivo. They have shown the ability to activate monocytes/macrophages, granulocytes, NK cells and T lymphocytes, especially helper T lymphocytes. Furthermore, positive effects were observed on the lysis of tumor cells by NK cells, as well as the induction of specific cytokines. Another relevant aspect is that *Viscum album* has the ability to stabilize DNA, reducing chromosomal damage and improving the repair function of genetic material. Inhibitory effects have been identified on the expression of genes related to tumor progression, as well as on the inhibition of cancer cell motility and invasion (KIENLE; KIENE, 2017). Based on this evidence, the use of *Viscum album* can be considered as a complementary treatment to conventional treatments, not replacing them (OSTERMANN et al., 2020).

Due to the anticancer effects of mistletoe, it is essential to understand the subtypes of *Viscum album* A, M and P and their respective clinical indications in viscotherapy. *Viscum album* type A (abieto) is recommended for tumors of the central nervous system, head, lung, prostate cancer, lymphoma, leukemia and multiple myeloma. This subtype has a lower lectin content and milder cytotoxicity, therefore being more appropriate for weakened cancer patients and children. *Viscum album* type M (apple tree) has a high content of lectins, making it more potent and cytotoxic in relation to tumor cells. It is indicated for breast cancer, gynecological cancer and abdominal tumors, and can be used in the elderly and more resistant patients. *Viscum album* type P (pine) has the highest concentration of lectins and is highly cytotoxic against tumors. It is considered the most effective for stimulating

the phagocytic effects of granulocytes, and is recommended for patients without debilitation and preferably males. Its indications cover malignant melanoma, sarcoma, testicular cancer, neck, head, lung, prostate, lymphoma and CLL cancer. *Viscum album* type P also demonstrates affinity with the neurosensory system, while type M is more related to the metabolic-locomotor system, and type A is located between types P and M (MÜNST et al., 2013).

Adverse drug reactions (ADRs) were classified as mild or moderate, with no reports of serious ADRs. Some ADRs included local reactions with a diameter greater than 5 cm or an increase in body temperature above 38°C (STEELE et al., 2015), which are included in Table 1. The objectives of complementary therapy with *Viscum album* extracts include improving health-related quality of life and reducing the occurrence of adverse events (AEs) associated with conventional cancer treatments (OEI et al., 2019a). It is important to emphasize that the use of mistletoe preparations is considered safe, as there are only isolated reports of hypersensitivity reactions in patients, and reports on possible excessive reactions in patients are rare (WROTEK et al., 2014). Furthermore, mistletoe extracts contribute to reducing the frequency of unwanted effects associated with conventional treatment, especially in relation to chemotherapy and radiotherapy. There is a reduction in symptoms of nausea, headache, depression, exhaustion, concentration difficulties, sleep disorders, irritability, dizziness and fatigue, at the same time as a significant increase in patients' quality of life (MÜNST et al., 2013).

Desirable adverse reactions	Frequency	Medical arrangements
Local inflammatory response: less than 5cm in diameter at the application site	Often (very common)	<ul style="list-style-type: none"> • Temporary mistletoe break; • Adjust the mistletoe dose; • Cold compress on site.
Fever below 38°C; Flu-like symptoms	Occasionally (common)	<ul style="list-style-type: none"> • Temporary mistletoe break; • Adjust the mistletoe dose; • Physical measurements.
Undesirable adverse reactions	Frequency	Medical arrangements
Lymphadenome-galy	Rarely (uncommon)	<ul style="list-style-type: none"> • Change application location.
Generalized itching, urticaria, rash, rhinitis, conjunctivitis, angioneurotic edema, dyspnea, bronchospasm	Occasionally (common)	<ul style="list-style-type: none"> • Stop the mistletoe; • Antihistamine treatment; • Desensitization.
Erythema multiforme	Only two suspected cases were reported	<ul style="list-style-type: none"> • Stop the mistletoe; • Antihistamine treatment.
Temporary dizziness	Rarely (uncommon)	<ul style="list-style-type: none"> • Adjust the mistletoe dose.

Table 1. Adverse events of subcutaneous *Viscum album*.

Adapted from MÜNST et al., (2013, p. 74);

It is important to highlight that, even after achieving complete remission of cancer, the use of mistletoe is indicated to prevent possible relapses. Furthermore, it is recommended in cases of pre-cancerous lesions, as the beneficial effects of *Viscum album* are not limited to the tumor alone, but extend to the entire immune system, including the bone marrow, with formative and self-regulatory purposes (MÜNST et al., 2013), according to the therapy steps described in Table 2. Patients' self-regulation, that is, the person's own ability to achieve balance and feel competent and safe in stressful situations, is significantly improved with mistletoe therapy. There are

also indications that adequate self-regulation may improve response to the other benefits of *Viscum album* therapy, such as increased vitality, well-being, nutritional health, weight, digestive function and warmth; KIENE, 2017).

Therapy steps	Significant indications	Therapeutic purpose
Adjuvant therapy	Prevent recurrence after conventional treatment	<ul style="list-style-type: none"> • Promotion of quality of life; • Increased survival.
Supportive therapy	Combined with chemotherapy and radiotherapy treatment	<ul style="list-style-type: none"> •Immune protection; •Increased tolerance to conventional treatments;
Palliative therapy	Incurable and metastatic neoplasms	<ul style="list-style-type: none"> •Promotion of quality of life; •Extended survival.
Prophylactic therapy (prevention)	Precancerous lesion	<ul style="list-style-type: none"> •Regression of the precancerous lesion.

Table 2. *Viscum album*: indications in oncological therapies

Adapted from MÜNST et al., (2013, p. 71);

VISCUM ALBUM: PROMISING RESULTS

The study titled “Quality of life in cancer patients treated with mistletoe: systematic review and meta-analysis” demonstrated that the use of *Viscum album* extracts resulted in clinically significant improvements. Patients with different types of cancer who received VAE applications reported an improvement in subjective well-being, leading to the conclusion that “VAE treatment is a viable complementary option to any anticancer treatment” (LOEF; WALACH., 2020).

In the review article by OEI et al., (2019a), it was systematically observed that, in a clinical study with eight cancer patients subjected to the application of *Viscum album* extracts, there was an increase in cytokine levels in the serum. In another clinical

trial involving 10 breast cancer patients, subcutaneous application of *Viscum album* lectins resulted in the stimulation of Natural Killer (NK) and T helper cells. Furthermore, a study with cultured glioblastoma cells demonstrated inhibition of tumor growth and a strengthening of NK cell-mediated lysis of glioblastomas, resulting from the action of *Viscum album* extracts. Other studies have also observed immunomodulatory effects, including neutrophilia, increased granulocyte phagocytic activity, and an increase in NK cells, as a result of a single intravenous infusion of *Viscum album* extracts. Furthermore, in a clinical trial of 98 breast cancer patients, intravenous administration of *Viscum album* extracts was shown to prevent surgery-induced suppression of oxidative burst activity in granulocytes. Another clinical trial with 62 patients diagnosed with colorectal cancer revealed that *Viscum album* extracts can prevent the suppression of NK cell activity (OEI et al., 2019b).

Doctor Iramaia Chaguri, specialized in anthroposophic medicine and gynecology-obstetrics, shared a clinical case in *Revista Arte Médica Ampliada* in 2017. The case involved a 63-year-old patient with multiple comorbidities, including morbid obesity and hypertension, who was diagnosed with endometrioid adenocarcinoma of endometrium for fifteen years. Due to his health conditions and associated risks, surgery was contraindicated from the beginning of follow-up. Initially, she received exclusive radiotherapy and follow-up care. Over time, the patient had two relapses, treated with chemotherapy based on carboplatin and paclitaxel. In 2016, she developed new symptoms, including vaginal bleeding, pelvic pain and serosanguineous discharge, accompanied by a significant increase in uterine volume. The biopsy confirmed a new recurrence of endometrioid adenocarcinoma.

Due to the stenosis of the cervical canal caused by the tumor, the patient could not undergo surgery, which put her at risk of uterine rupture and uncontrollable bleeding. She was referred for chemotherapy, but due to reports of success in the use of high doses of intratumoral *Viscum album* in stenosing tumors in other regions of the body, the same approach was proposed while waiting for chemotherapy to begin. Four weekly intratumoral applications of Helixor P were performed, with progressively higher doses, and subcutaneous applications of Helixor P three times a week. Ultrasound monitoring demonstrated successful applications, with significant improvement within two weeks. The initial uterine volume of more than 1,000 cm³ reduced to 344 cm³ after the applications, maintaining the endometrial echo. The patient experienced an improvement in her well-being and elimination of serosanguineous material. After the applications, the patient had not started chemotherapy, but her emergency condition was resolved. The last examination, after chemotherapy treatment, showed a uterus with a volume of 138 cm³. This case highlighted the effectiveness of *Viscum album*'s therapeutic potential in a situation where surgery was not feasible due to cervical stenosis caused by the tumor, reporting that intratumoral applications of *Viscum album* have been considered promising due to the ability to administer high doses of this compound directly to the tumor, minimizing systemic side effects. As the effectiveness in destroying cancer cells

and inducing programmed death appears to be dose related, this method may provide a significant benefit in the use of *Viscum album*.

CONCLUSION

Throughout this study, we explored the role of *Viscum album* as a complementary therapy in cancer treatment. Our comprehensive analysis of the literature and review of clinical studies allowed us to understand the potential effects of mistletoe on the quality of life and therapeutic response of cancer patients. The results of this research highlight that the use of mistletoe extracts has been shown to promote clinically significant improvements in the quality of life of cancer patients, alleviating adverse symptoms and providing subjective well-being. We note that mistletoe has immunomodulatory properties that can positively influence the immune system's response to disease.

However, it is essential to recognize that mistletoe must not be considered a stand-alone therapy for cancer, but rather a complementary option that can be integrated into conventional approaches. Importantly, further research, preclinical trials, and in vitro and in vivo clinical trials are needed to fully clarify the mechanisms of action of VA and its effectiveness in different types of cancer. As research continues to advance, we hope that mistletoe can be better integrated into clinical practice, benefiting oncology patients and contributing to an anthroposophic, integrative and complementary approach to fighting cancer.

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