

Preclinical report

Absence of tumor growth stimulation in a panel of 16 human tumor cell lines by mistletoe extracts *in vitro*

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Extracts of *Viscum album* (mistletoe) are widely used as complementary cancer therapies in Europe. The mistletoe lectins have been identified as the main active principle of mistletoe extracts. They have been shown to exhibit cytotoxic effects as well as immunomodulatory activities. The latter is exemplified by induction of cytokine secretion and increased activity of natural killer cells. Recent reports however, indicated possible tumor growth stimulation by mistletoe extracts. Therefore, the three aqueous mistletoe extracts (Iscador M special, Iscador Qu special and Iscador P) were evaluated for antiproliferative and/or stimulatory effects in a panel of 16 human tumor cell lines *in vitro* using a cellular proliferation assay. The results show no evidence of stimulation of tumor growth by any of the three Iscador preparations, comprising central nervous system, gastric, non-small cell lung, mammary, prostate, renal and uterine cancer cell lines, as well as cell lines from hematological malignancies and melanomas. On the contrary, Iscador preparations containing a high lectin concentration (Iscador M special and Iscador Qu special) showed antitumor activity in the mammary cancer cell line MAXF 401NL at the 15 µg/ml dose level with a more than 70% growth inhibition compared to untreated control cells. In addition, a slight antitumor activity (growth inhibition 30–70%) was found in three tumor cell lines for Iscador M special and in seven tumor cell lines for Iscador Qu special, respectively. Iscador P, which contains no mistletoe lectin I, showed no antiproliferative activity. [© 2002 Lippincott Williams & Wilkins.]

Key words: Antiproliferative activity, human tumor cell lines, mistletoe extracts, stimulation of tumor growth.

Introduction

Aqueous extracts of the European mistletoe (*Viscum album* L.) have been widely used for decades as alternative treatment and adjuvant cancer therapy, particularly in Germany, Austria and Switzerland.^{1–3}

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The main components of mistletoe extract are lectins, viscotoxins and alkaloids. The mechanism of action is probably 2-fold. On the one hand, mistletoe lectins can stimulate immunological relevant effector cells like macrophages, natural killer cells, and B and T lymphocytes with subsequent release of cytokines [interleukin (IL)-1, IL-6, IL-10, tumor necrosis factor- α and granulocyte macrophage colony stimulating factor];^{4–8} on the other hand, mistletoe lectins have shown direct growth inhibitory effects on tumor cells. Depending on the concentration, treatment with mistletoe lectins results in death via apoptosis or necrosis.^{9–13} Moreover, preclinical activity of aqueous mistletoe extracts has been shown in transplantable murine tumor models *in vivo*.¹⁴

In particular, the stimulation of immunological effector cells could be also associated with a potential growth stimulatory effect on hematological malignancies which are derived from the immune system like non-Hodgkin's or Hodgkin's lymphomas as well as acute leukemias. There is a case report that mistletoe extracts can enhance the growth of non-Hodgkin's lymphomas.¹⁵ The majority of patients, however, appear to have benefited from an additional therapy with mistletoe.^{1–3} Furthermore, Gabis *et al.* described stimulation of melanoma and sarcoma cell lines by a purified mistletoe lectin *in vitro*.¹⁶

One of the oldest mistletoe preparations is Iscador. Iscador is extracted from mistletoe plants growing on different host trees like apple (Iscador M special), oak (Iscador Qu special) and pine (Iscador P). The aqueous extracts are biologically and biochemically standardized. Iscador M special contains 250 ng total lectins/ml, Iscador Qu special contains 375 ng total lectins/ml, whereas Iscador P contains only trace amounts of lectins.