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Anticarcinogenic and antimetastatic activity of Iscador

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Methylcholanthrene-induced sarcoma formation in mice was found to be effectively inhibited by the intraperitoneal injection of mistletoe extract (Iscador M). Induction of sarcoma and sarcoma-induced death were inhibited completely at a concentration of 1 mg Iscador/dose. The concentration needed for 50% inhibition was found to be 0.0166 mg Iscador/dose. Mistletoe extract was also found to inhibit lung metastasis induced by B16F10 melanoma cells in mice. Simultaneous administration of the *Viscum album* extract inhibited lung nodule formation by 92.0% and produced a 71.3% increase in life span.

Keywords: Tumour cells, mistletoe, mice, lung metastasis, survival.

Introduction

Inhibition of recurrence of tumours was reported by several workers using mistletoe therapy [1]. Although the exact mechanism of this inhibition is unclear, several theories could be proposed: (1) the cytotoxic activity of Iscador [2,3] removes residual cells left after chemotherapy and radiation; (2) the immunomodulatory activity of Iscador [4] will induce immunocompetent cells that may specifically destroy cancer cells; (3) it may be possible that Iscador induces a differentiation of tumour cells, thus making them less proliferative and apoptotic [5]; and (4) Iscador may inhibit the cascade of events that will lead to tumour cell progression and metastasis.

Skin carcinogenesis is a perfect model for following the events that ultimately result in transformation of a cell leading to an undifferentiated tumour. Material that could inhibit the carcinogenesis might be useful in differentiation therapy for suppression of a tumour. In this review we show that administration of Iscador inhibits carcinogenesis produced by 20-methylcholanthrene as well as B16F10 melanoma-induced lung metastasis.

Materials and methods

Female Swiss Albino mice were used for carcinogenesis experiment (15 animals per group) and C57BL/6 mice for antimetastatic studies (8–10 animals per group; experiments repeated three times). Sarcoma was developed on the dorsal surface of the mice by injecting a single dose of 20 μg 20-methylcholanthrene (ICN Pharmaceuticals, New York, USA) per mouse. Sarcoma development and survival were monitored up to 180 days. The bacterially fermented *Viscum album* extract Iscador M (5%; Weleda AG, Arlesheim, Switzerland), produced from mistletoes grown on apple trees, was administered as shown in Table 1. Lung metastasis was induced by injecting 10^6 viable B16F10 melanoma cells (National Faculty for Animal Cell and Tissue Culture, Pune, India) through the lateral tail vein. Animals were sacrificed after 21 days to determine the lung tumour colonies. Survival of the mice was determined as well.

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Results

Administration of Iscador significantly reduced the sarcomas developed in the animals by 20-methylcholanthrene administration (Table 1). However, only one animal developed sarcoma within an observation period of 160 days, while all of the control mice developed sarcoma within 80 days. Although these values represent data from experiments using 1.66 mg *Viscum album*/dose, the effect of Iscador was seen at even lower concentrations and 50% death could be inhibited at concentrations of 1/100th of this concentration (16.6 μg *Viscum album*/dose), indicating the efficacy of the drug.

As shown in Table 2, administration of Iscador reduced the metastasis of B16F10 melanoma into the mice lungs. Simultaneous application of the drug was more effective, inhibiting 92.0% of the lung tumour colonies in

Table 1. Effect of mistletoe therapy on methylcholanthrene-induced sarcoma in mice

	Animals developing sarcoma		Animals surviving	
Days	Control	Treated	Control	Treated
40	8/15	0/15	15/15	15/15
80	15/15	0/15	8/15	15/15
120	15/15	0/15	2/15	15/15
160	15/15	1/15	0/15	15/15

A single dose of methylcholanthrene (200 μg/0.1 ml) was injected subcutaneously on the dorsal side of the mice. *Iscador* M (5%; 1.66 mg, as 0.1 ml/mouse) was injected twice weekly for 15 weeks. The mice (15 per group) were observed for tumours and survival for 6 months.

Table 2. Effect of *Iscador* on lung colony formation induced by B16F10 melanoma cells

Iscador treatment	Number of lung tumour colonies	Inhibition of lung tumour colonies (%)	Increase in life span (%)
No treatment	250	–	–
Prophylactic administration	53.5 ± 7.68	78.6	37.1
Simultaneous administration	20.0 ± 10.0	92.0	71.8
After tumour development	79.0 ± 7.6	68.2	30.9

B16F10 melanoma cells (10^6/animal) were injected through the lateral tail vein. *Iscador* (1.66 mg/dose) was injected as three different modalities: (1) prophylactic: 5 days prior to the tumour inoculation and continued for 5 more days; (2) simultaneously: *Iscador* was given along with metastatic cells for 10 days; (3) after tumour development: 5 days after tumour induction and continued for 10 days. Animals (8–10 per group) were sacrificed 21 days after tumour inoculation.

mice. Prophylactic administration was also effective, inhibiting 78.6% of lung colonies, while colony number was significantly reduced even in developed tumours. Iscador administration was also found to reduce death due to tumour burden in the animals. Thus, the life span increased to 71.8% in the group treated simultaneously with the drug.

Lung hydroxyproline and sialic acid, which are markers of lung metastasis, were considerably reduced in the animals treated with Iscador. The values for hydroxyproline were 1.05 ± 1.2, 29.9 ± 6.6, and 7.53 ± 1.9 μg/mg protein for normal, lung from untreated animals and lung from Iscador-treated mice, respectively. The sialic acid values were 2.25 ± 0.2, 4.76 ± 0.86, and 3.73 ± 0.06 μg/μl serum, respectively.

Discussion

The mechanisms of the inhibition of chemical carcinogenesis and metastasis could not be explained by present theories of *Viscum album* effects. While the inhibition of metastasis may be explained on the basis of tumour suppression by an immunostimulation induced by Iscador, the inhibition of chemical carcinogenesis may be explained by a yet undefined interference of the drug with an activation or promotion of oncogenesis. An alternative explanation is that the drug is able to induce differentiation of tumour cells or reduce their viability by apoptotic cell death.

However, the results presented in this review further point to the use of Iscador in differentiation therapy against cancer, especially after removing the tumour burden after surgery or chemotherapy.

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