

Mistletoe: a story with an open end

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Treatment with *Viscum album* L., the white berry mistletoe, is one of the most widely used unconventional cancer therapies in Europe, and is now gaining attention beyond the boundaries of anthroposophic medicine. An obvious discrepancy between the popularity of mistletoe extracts and their classification as a non-conventional treatment modality with unproven efficacy in oncology was stated by Gabius *et al.* [1]. However, studies in cancer patients have shown significant increases in immunological parameters, and some 50 clinical studies (historical, retrospective, prospective and randomized) report extended survival times, improved quality of life or, in some studies, tumour regression with mistletoe therapy. Although the average quality of the trials appears to be rather poor, several studies indicate significant results [2,3].

The first chapter of the mistletoe story was written by Plinius who reported that Celtic druids respectfully cut off mistletoes from trees with a golden sickle. Mistletoes were believed to promote pregnancy and to cure every illness as an *omnia sanans* [4]. Later, Hippocrates and also Arabian physicians applied mistletoes in the case of epilepsy, 'weakness of the heart', oedema, and diseases of the spleen. Similar indications are handed down to the homeopathic *materia medica* today [5].

The next chapter was written by Rudolf Steiner who recommended mistletoe preparations for the treatment of carcinomas [6]. Even now, anthroposophical doctors inject *Viscum album* L. extracts produced under complicated manufacturing processes using the mixed sap of mistletoes harvested separately in winter and in summer time.

Proceeding from the clinical experience, mistletoe has been extensively investigated. During the 1960s, Vester and Nienhaus [7] isolated and purified carcinostatic protein fractions from *Viscum album* L. which were recognized as viscotoxins and mistletoe lectins. Franz *et al.* [8], Stirpe *et al.* [9] and Olsnes *et al.* [10] comprehensively investigated the effects of mistletoe lectins on tumour and immune cells. The effects of basic polypeptides (specifically the viscotoxins) were reported by Rossel and Samuelsson [11] and Konopa *et al.* [12]. Apart from the toxic proteins, several other active substances, such as oligosaccharides and polysaccharides, were de-

scribed. In addition, *Viscum album* L. products contain free amino acids, vitamin C, triterpene, and flavonoids whose contribution to the effects of the whole plant extract are unclear.

Later on, several groups added some new chapters to the mistletoe story. The cytotoxicity of *Viscum album* L. extracts and mistletoe lectins was investigated by Hülsen *et al.* [13], Doser *et al.* [14], Ribéreau-Gayon *et al.* [15] and Dietrich *et al.* [16]. The stimulation of natural killer cell-mediated cytotoxicity was investigated by Müller and Anderer [17,18] for a rhamnogalacturonan from *Viscum album* L. and by Hajto *et al.* [19] for mistletoe lectin-I, while Kuttan and Kuttan [20] and Kuttan [21] observed a stimulation of macrophage-mediated cytotoxicity by a cytotoxic 5 kDa peptide (NSC 635 089). Simultaneously, the immune responses of cancer patients treated with mistletoe extracts and purified components were described by Stettin *et al.* [22], Beuth *et al.* [23], Heiny and Beuth [24], Hajto *et al.* [25] and Hülsen *et al.* [26]. However, although it is generally accepted that a restoration of an altered immune system is of benefit for cancer patients, it remains to be shown that the stimulation of immune cells by subcutaneously applied plant antigens will elicit a sufficient antitumour response.

Nowadays, several groups of researchers are adding exciting new chapters to the mistletoe story. Therefore, various participants of an International Meeting on the subject in Herdecke, Germany, in October 1996 were invited to review their special field of research on mistletoes. The main active principles (specifically mistletoe lectin-I versus whole plant extract) and their mechanisms are the subject of intensive discussion. This special issue of *Anti-Cancer Drugs* presents a state-of-the-art review.

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