Christian Academy of Natural Health

MATERIA MEDICA III

Mistletoe (*Viscum album L.*)

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Principal Proposed Uses: Antineoplastic, immunostimulant

Other Proposed Use: Antihypertensive

Overview

The major use of mistletoe, Viscum album, is as a palliative cancer therapy. Historically it has been used to treat hypertension, epilepsy, exhaustion, anxiety, arthritis, vertigo, and degenerative inflammation of the joints. V. album is the European mistletoe species; it is the species used in the treatment of cancer and it will be the focus of this monograph.

Phoradendron, or American mistletoe, is rarely used medicinally. Both species contain lectins, protein toxins, and polysaccharides. The scientific evidence regarding

mistletoe's use as a palliative cancer therapy is inconclusive but promising. Mistletoe extracts are usually given parenterally and may cause inflammation at the injection site. Side effects from ingestion of mistletoe include gastrointestinal symptoms such as nausea, vomiting and diarrhea. Poisonings of children after mistletoe ingestion have been reported. There are no data on mistletoe's safety during pregnancy or lactation.

Historical and Popular Uses

Washington Irving described the tradition of stealing a kiss under this intriguing plant: "...the mistletoe, with its white berries," he said, is "hung up, to the imminent peril of all the pretty housemaids." At Christmas, the young men had the privilege of kissing ladies under mistletoe, "plucking each time a berry from the bush." Once all the berries had been plucked, no more kissing was allowed[1].

First described by the Greek naturalist Theophrastus in the Third Century BC, mistletoe became embedded in European rituals, folklore, and folk medicine. It was a sacred plant of the Celtic peoples who dominated Europe in the first millennium BC. The Gauls and the Celts called it "all-healer" or "cure-all"[2].

Both European and American mistletoe contain toxic proteins which are similar in their chemical composition and produce similar effects, including hypotension, bradycardia, and vasoconstriction, in test animals[3]. Despite the popular belief that the two types of mistletoe have opposite effects, the stems and leaves of these plants contain similar phytochemicals[4]. Anthroposophist Rudolf Steiner introduced the use of mistletoe extracts for the treatment of cancer in 1916[5]. Nowadays, Europeans include V. album in oncology therapies under the trade names Iscador and Helixor. The German Commission E has approved mistletoe as a treatment for degenerative and inflamed joints and as a palliative therapy for malignant tumors.

Botany

Medicinal species: Viscum album

Common names: All heal, bird lime, birdlime mistletoe, devil's fuge, European mistletoe, golden bough, herb de la croix (Fr), lignum crucis, mystyldene, visci albi fructus (berrie s), visci albi herba (leaves), visci albi stipites (stem), and viscum[6-10]

Botanical family: Loranthaceae[11]

Plant description: Mistletoe is a semi-parasitic woody perennial commonly found growing on oaks and other deciduous trees[7,10]. The plant is small, dioecious and shrubby, with oblong evergreen leathery entire leaves, clear dichasial branching and four-part flowers which form white sticky berries. It has a faint but characteristic odor and a bitter taste[8]. Viscum is most commonly seen on old apple, ash, and hawthorn trees; although mistletoe does not grow as well on oak trees, mistletoe from oak trees has traditionally been the most commonly used[12]. Mistletoe is propagated by birds that eat the berries and then excrete the seeds, or smear them on branches by wiping the sticky pulp off their beaks. Under proper conditions, the seeds germinate and the roots

penetrate the branch of the host tree. Mistletoe is considered a semiparasitic plant because it synthesizes its own chlorophyll but depends on the host for its supply of water and minerals. The parts used medicinally are the leaves and stems.

Where it's grown: V. album is native to Europe and Asia. Imports originate in Bulgaria, Turkey, the former Yugoslavia, Albania and the former USSR[8]. V. album grows in Europe, northwest Africa, and southwest and central Asia and Japan; the Asian plant is a special variety, V. album (L) var. coloratum. V. album is grown in the US in Sonoma County, California; it is not imported[13]. American mistletoe grows in the eastern US from New Jersey to Florida, and from southern Ohio to southern Indiana. It is prevalent in Texas and some species are common in California and Oregon.

Biochemistry

Mistletoe (Viscum album): Active Chemical Constituents

· Glycoproteins: mistletoe lectins I (galactoside-specific lectin), II, and III

· Proteins: viscotoxin

· Polysacchrides: galacturonan, arabinogalactan

· Alkaloids

Mistletoe's lectins are cytotoxic glycoproteins of approximately 10,000 molecular weight; they cause cells to agglutinate[14] and inhibit protein synthesis on the ribosomal level. The lectins, also known as viscumin or agglutinin, are dual chain molecules. Chain A inhibits protein synthesis and chain B activates macrophages and releases lymphokines from lymphocytes. Both the A and B chains of mistletoe lectin I also inhibit allergen-induced histamine release from leukocytes and collagen-induced serotonin release from platelets[14]. Lectins are structurally similar to two highly biologically active toxic proteins, ricin and abrin. The amounts and biological activity of V. album lectins are dependent on the host tree, manufacturing process, and time of harvest[15].

Viscotoxin is a 46-amino acid peptide that damages cell membranes. Viscotoxin is found only in V. album. A similar constituent of Phoradendron is phoratoxin, a polypeptide about twice the weight of viscotoxin; it makes up 0.01% to 0.23% of Phoradendron leaves and stems[16].

Various polysaccharides are thought to be involved in mistletoe's antineoplastic effects.

The leaves and stems contain esterified galacturonan, while the berries contain primarily arabinogalactan[17].

Alkaloids are nitrogenous compounds that may contribute to mistletoe's cytotoxicity[14].

Experimental Studies

Mistletoe: Potential Clinical Benefits

1. Cardiovascular: Hypertension

i. In vitro data: none

ii. Animal data: Animal experiments are contradictory[8].

iii. Human data: A small case series in hypertensive adults treated with an herbal combination including V. album reported decreased blood pressure over 3-5 months.

Since an herbal combination was used, it is difficult to interpret the effects of V. album alone[18]. There are no controlled trials evaluating V. album as a sole antihypertensive or comparing it to standard medications.

2. Pulmonary: none

3. Renal and electrolyte balance: none
4. Gastrointestinal/hepatic: none

5. Neuro-psychiatric: Epilepsy, exhaustion, vertigo, and anxiety: Traditional uses, no data[10].

6. Endocrine: none

7. Hematologic: Coagulant : Traditional use, no data[10].

8. Rheumatologic: Degenerative inflammation of the joints: Traditional use, no data[8].

9. Reproductive: Abortifacient: Phoradendron has been recommended by herbalists as an abortifacient. No data are available.

10. Immune modulation: Immunostimulant

i. In vitro data: V. album agglutinin, a galactoside-specific plant lectin, induced apoptosis in human and murine lymphocytes and monocytes[19] and stimulated the proliferation of hematopoietic progenitor cells from healthy volunteers[20]. Mistletoe extracts induced proliferation of peripheral blood mononuclear cells; the strongest proliferation was seen with mistletoe from apple trees[21]. CD4+ T cells exposed to mistletoe extract displayed a significant increase in mean velocity, time locomoting, and migration distance[22,23].

ii. Animal data: none

iii. Human data: Case series and controlled trials in healthy adults and cancer patients support the use of mistletoe as an immunostimulant. In six healthy volunteers given mistletoe extract for eight weeks, there was pronounced proliferation of peripheral mononuclear cells[24]. See also Antineoplastic.

11. Antimicrobial: none

12. Antineoplastic: Antineoplastic

i. In vitro data: Mistletoe lectins cause both apoptosis and direct cytotoxicity[25]. Mistletoe lectins triggered apoptosis and enhanced the cytotoxic effect of chemotherapeutic drugs in leukemic cell lines[26]. V. album extracts had significant cytotoxic activity against cultured Hep-2 cells[27]. Mistletoe (Iscador) inhibited the growth of rat hepatoma cells and Molt 4 cells in tissue culture[28]. Mistletoe lectins inhibited the growth of the Molt 4 tumor cell line; mistletoe lectin III was the most potent inhibitor[29]. Normal Molt 4 cells and three drug-resistant sublines were sensitive to the cytotoxic effects of Helixor[30].

Mistletoe lectins I, II, and III exerted cytotoxic effects against six human breast cancer cell lines[31]. All mistletoe lectins inhibited leukemia cell growth; mistletoe lectin III was approximately ten times as cytotoxic as lectin I[32].

Mistletoe extract significantly reduced the DNA damaging effects of carcinogens[33].

In a study comparing 12 different mistletoe preparations on human leukocytes, the different preparations had varying effectiveness in inducing apoptosis and cytokine production. However, there was no correlation between the biological effects and the lectin content of these different preparations[34].

ii. Animal data: The Viscum album preparation Isorel significantly restored the suppressed immune response of fibrosarcoma-bearing mice[35]. Mistletoe preparations were effective in fighting solid tumors in eight of ten animal studies (seven in mice and three in rats). In two studies in mice, an ext ract of V. album coloratum (Korean mistletoe) significantly inhibited metastases including lung metastases[36,37]. Iscador M, an extract of Viscum album, inhibited metastatic colony formation induced by melanoma cells and reduced mortality in mice[38]. When Iscador was administered to mice simultaneously with melanoma cells, lung nodule formation was inhibited by 92% and there was a 71% increase in life span[38]. Mistletoe lectin I significantly reduced tumor volume in rats with glioma[39]. It reduced tumor volume and lung and liver metastases in mice[40]. A single injection of the V. album preparation Isorel reduced tumor size and caused tumor necrosis[41]. Another mistletoe preparation had antimetastatic activity against B16 melanoma lung colonization[42].

In two negative studies in rats, mistletoe lectin I did not inhibit chemicallyinduced bladder cancer[43,44], and did not stimulate significant cellular immunological reaction in the wall of normal or cancerous urinary bladder[43].

iii. Human data: In case series and controlled trials, mistletoe had immunostimulant effects in cancer patients. Studies of its effects aga inst cancer have had conflicting results.[45-49]

In several small case series, cancer patients given parenteral V. album preparations (in doses ranging from 0.5 ng/kg to 1 mg/kg) had increases in natural killer cells, T-helper cells, cytokine release, and peripheral blood mononuclear cells and lymphocytes. In one of these series, V. album treatment was associated with an improved quality of life[48].

In a prospective randomized clinical trial of 35 patients with stage II-IV glioma, the treatment group received standard treatment plus a mistletoe extract (1 ng mistletoe lectin I/kg twice weekly) for three months beginning the day after surgery. The control group received standard therapy. The group receiving mistletoe had a significant upregulation of cell counts (CD 3, CD-4, and CD-8 cells) and activities (CD-25, HLA/DRpositive cells) after three months compared to preoperative values, whereas the control group remained at preoperative values[50].

In a prospective randomized clinical study of 47 breast cancer patients, those given mistletoe lectin I (0.5-1.0 ng/kg twice weekly) had enhanced activity of peripheral blood natural killer cells and T–lymphocytes[15].

Studies of mistletoe's antineoplastic effects have had conflicting results. A 59-year-old man with small cell lung carcinoma opted for Iscador treatment rather than chemotherapy. He received subcutaneous Iscador once daily for five days, followed by oral Iscador 0.05–0.1 mg three times a day. The dose was progressively increased over a few weeks to achieve a maintenance dose of 5-10 mg three times a day. Subsequently radiotherapy was given and the patient lived five and a half years.[51]

In 16 patients with stage III or IV ductal pancreatic carcinoma, Eurixor (1 ng/kg) was administered twice weekly by subcutaneous injection. No partial or complete remissions were seen, but all but two patients claimed that mistletoe had a positive effect on their quality of life, with a decline only in the last few weeks of life[52].

Fourteen patients with untreated stage IV renal adenocarcinoma and lung metastases were treated with escalating subcutaneous doses of Iscador over three weeks. All the patients died, and no response to treatment was noted[53]. In a retrospective analysis of 991 patients with colorectal cancer, mistletoe treatment significantly decreased the recurrence rate by 13% in those with lymph node negative disease, and by 23% in those with lymph node positive disease, in comparison to the untreated group. The survival probability as a result of the mistletoe therapy was 340 days longer than in the untreated group[54].

13. Antioxidant: none

14. Skin and mucus membranes: none

15. Other/miscellaneous: none

Toxicity and Contraindications

All herbal products carry the potential for contamination with other herbal products, pesticides, herbicides, heavy metals, and pharmaceuticals. This is particularly concerning with imports from developing countries. Furthermore, allergic reactions can occur to any natural product in sensitive persons.

Allergic reactions to mistletoe have been reported. A case of allergic rhinitis has been reported in a subject handling commercial mistletoe tea[7]

Potentially toxic compounds in mistletoe: Lectins, viscotoxin. All parts of the plant contain toxic compounds.

Acute toxicity: The German Commission E reports side effects such as chills, fever, headaches, angina and hypotension[9]. Ingestion of the American Phoradendron species usually causes acute gastrointestinal symptoms; lectins in both Viscum and Phoradendron species may cause delayed gastroenteritis. Ingesting concentrated mistletoe extracts may produce serious poisonings. Symptoms of acute toxicity include nausea, diarrhea, fixed and dilated pupils, diplopia, irritated conjunctiva, bradycardia, vasoconstriction, hypo- or hypertension, seizures, delirium and hallucinations. Cardiac arrest may occur. Deaths have occurred after ingestion of mistletoe tea taken as a tonic or abortifacient[55-59].

In 300 cases of ingestion of mistletoe leaves or berries, the majority of patients remained asymptomatic and no deaths occurred; ingestion of up to three berries or two leaves is unlikely to produce serious toxicity[7]. Of the 1754 exposures to Phoradendron leucarpum reported between 1955-1992, no fatalities occurred, and 90.3% of those exposed remained asymptomatic. Children accounted for 92.1% of the cases[60].

Intradermal injection of mistletoe may cause local inflammation, which can develop into necrosis[8].

Chronic toxicity: Lectins are cytotoxic by inhibiting protein synthesis at the ribosomal level[14, 61, 62]. One case of hepatitis has been reported after ingestion of an herbal compound containing mistletoe, but no other instances of hepatotoxicity have been documented for mistletoe, and hepatitis has been documented with a common contaminant of scullcap, which was also in the herbal compound[11].

Limitations during other illnesses or in patients with specific organ dysfunction:

Herbalists recommend avoiding mistletoe in patients with chronic progressive infections such as tuberculosis. Persons with heart disease should be monitored when using mistletoe, because it may cause hypertension or hypotension.

Interactions with other herbs or pharmaceuticals: Mistletoe may interfere with existing cardiac or immunosuppressant therapies[11]. Mistletoe is contraindicated in patients taking monamine oxidase (MAO) inhibitors because mistletoe preparations contain tyramine[14].

Safety during pregnancy and/or childhood: Mistletoe has not been approved for pediatric use or use during pregnancy or lactation. It is contraindicated during pregnancy due to its speculated uterine stimulant action[63].

Typical Dosages

Provision of dosage information dose NOT constitute a recommendation or endorsement, but rather indicates the range of doses commonly used. Doses are given for single agent use and must be adjusted when using remedies in combinations. Doses may also vary according to the type and severity of the condition treated and individual patient conditions.

Typical adult doses:

Dosing parameters have not been established. Dosage depends on a number of factors including as the host tree, the preparation method, and standardization of the product to a particular constituent. Overdoses may cause poisoning.

Tea (cold water infusion): Cold water poured over 2.5 g (1 tsp.) of finely chopped drug and allowed to stand at room temperature for 10 to 12 hours, then strained. One to two cups daily. Mistletoe is also available in tea bags[9]

Tincture (1:5 in 45% alcohol): 1-4 ml daily[12,64].

Dried aqueous extract (4:1): 100-250 mg daily[12]

Fluid extract (1:1 in 25% alcohol): 1-3 ml three times daily[11]

"Blood pressure tea": Mistletoe leaves, hawthorn leaves and flowers, and melissa leaves in equal parts. Two cups daily prepared by infusing 2 teaspoons of the mixture for five to ten minutes[65].
Oral Iscador: The following regime was used in one case study: 0.05-0.1 mg three times daily, then titrated over two weeks to 5-10 mg three times daily[51].

Parenteral preparations with standardized concentrations of mistletoe lectin I: 0.29-12 ng/kg per day[48,66]. In some studies the optimal dose was considered to be 1 nanogram per kilogram given twice weekly[48,52, 67].

Parenteral fresh plant extract: Based on whole fresh plant, dosages have ranged from 1 to 200 mg subcutaneously daily for up to two years. IV doses ranging from 0.09 to 0.33 mg per kg per day of fresh plant equivalent have been given as single or daily doses in 250 ml of saline[49].

Pediatric dosages: Unknown

Brand names: European brands include: Iscador and Helixor, for subcutaneous use in cancer treatment, and Plenosol, for parenteral use for arthritic joints[65,68].

Availability: Injectable forms are available only in Europe. Powdered herb capsules are available in the US3. While Iscador is not commonly used in the US, and is not approved for sale in the United States, but US doctors can order it directly from European manufacturers.

American patients may also travel to Europe for Iscador treatment. Mistletoe therapy is available at clinics, hospitals, and private practices in the United Kingdom, Switzerland, West Germany, and the Netherlands[2].

Dosages used in combinations: Mistletoe is a component of antihypertensive medications, cardiotonics and sedatives. Except for the mistletoe tea combination noted above, the mistletoe dosages used in these combinations are unknown[8].

This concludes this course lesson sample.