Mistletoe

Species (Family)

Viscum album L. (Loranthaceae)

Synonym(s)

Viscum

Part(s) Used

Leaf, fruit (berry), twig

Pharmacopoeial and Other Monographs

BHP 1996[G9]
Complete German Commission E[G3]
Martindale 32nd edition[G43]
PDR for Herbal Medicines 2nd edition[G36]

Legal Category (Licensed Products)

Mistletoe is not included in the GSL.[G37]

Constituents[G2,G22,G64]

Acids Fatty acids (C_{12}–C_{22}), 80% oleic and palmitic;[1] phenolic acids (e.g. anisic, caffeic, *p*-coumaric, ferulic, gentisic, myristic, *p*-hydroxybenzoic, *p*-hydroxyphenylacetic, protocatechuic, shikimic, sinapic, quinic, vanillic).[1,2]

Alkaloids[3] It has been suggested that alkaloids can be passed on from hosts to parasitic plants like mistletoe (e.g. nicotine alkaloids have been isolated from mistletoe growing on Solanaceae shrubs).[4]

Amines Acetylcholine, choline, β-phenylethylamine, histamine, propionylcholine and tyramine.[5]

Flavonoids Flavonol (e.g. quercetin) derivatives,[3] chalcone derivatives[6] and flavonone derivatives.[6]

Lectins Mixture of high molecular weight polypeptides. Quoted molecular weights include 160 000,[7] 115 000 (four chains)[7,8] and 60 000 (two chains).[9] Three lectins have been isolated which possess either two chains (LII, LIII) or four chains (LI).[10]

Terpenoids β-Amyrin, betulinic acid, lupeol and ester combinations, oleanolic acid, resin acids, ursolic acid, β-sitosterol, dihydro-β-sitosterol, stigmasterol, sterol A and phytosterol glucoside.[6,11]

Viscotoxins Mixture of low molecular weight polypeptides including the pure proteins viscotoxins A_2, A_3 and B.[12–14]

Other constituents Mucilage, polyols (e.g. mannitol, dulcitol, xylitol, inositol, pinitol, quebrachitol, quercitol),[15] sugars (e.g. fructose, glucose, raffinose, sucrose),[13] starch, syringin (a phenolic glucoside)[6] and tannin.

Food Use

Mistletoe is not generally used as a food. The branches and berries of mistletoe are listed by the Council of Europe as natural sources of food flavouring (category N3).[G16] This category indicates that mistletoe may be added to foodstuffs in the traditionally accepted manner, although there is insufficient information available for an adequate assessment of potential toxicity.

Herbal Use

Mistletoe is stated to possess hypotensive, cardiac-depressant and sedative properties. Traditionally, it has been used for high blood pressure, arteriosclerosis, nervous tachycardia, hypertensive headache, chorea and hysteria.[G2,G7,G64]

Dosage

Dried leaves 2–6 g or by infusion three times daily.[G7]

Liquid extract 1–3 mL (1 : 1 in 25% alcohol) three times daily.[G7]

Tincture 0.5 mL (1 : 5 in 45% alcohol) three times daily.[G7]

Infusion 40–120 mL (1 : 20 in cold water) daily.[G7]

Soft extract 0.3–0.6 mL (1 : 8 infusion or tincture) three times daily.[G7]

Pharmacological Actions

Documented pharmacological studies for mistletoe have concentrated on the cytotoxic and immunostimulant properties of the plant. The pharmacological actions of mistletoe have been reviewed extensively.[4,5,12,16,17]

In vitro and animal studies

Much has been documented concerning the possible role of mistletoe in the treatment of cancer, in particular, a proprietary product Iscador, which is produced from naturally fermented mistletoe plant juice. The immunostimulant and cytotoxic effects exhibited by mistletoe are thought to play an important role in the cancerostatic action.[18]

Cytotoxic activity Cytotoxic activity has been exhibited both *in vitro* and *in vivo* by the crude plant juice, Iscador, glycoprotein fractions (lectins, viscotoxins) and alkaloid fractions.[3,18,19] Significant antitumour activity has been observed *in vivo* for mistletoe extracts against murine tumours, Lewis lung carcinoma, colon adenocarcinoma 38, and C3H mammary adenocarcinoma 16/C.[4] Researchers in Korea have isolated cytotoxic alkaloids from twigs and leaves of Korean mistletoe (*V. album*) with activity reported against L1210 (*in vitro*) and P388 (*in vivo*) test systems.[3] The authors commented that preliminary studies indicated the presence of some of these cytotoxic alkaloids in the European mistletoe (*V. album*). The anticancer activities of various mistletoe extracts and the contribution of the alkaloidal components towards this activity has been reviewed.[4] Alkaloidal components in mistletoe are thought to form glycoconjugates with lectins and viscotoxins, and help maintain the specific structures of these molecules necessary for therapeutic activity.[4]

The mode of action for cytotoxic activity of mistletoe has been linked to the ability of the basic amino acids present in mistletoe to maintain cell differentiation.[18] Sensitivity to mistletoe extracts has been documented for acute lymphoblastic leukaemia cells resistant to methotrexate and cytarabine.[20]

The optimum dose of Iscador for tumour inhibition in mice weighing approximately 30 g, has been estimated at 0.11 mg and 0.153 mg.[18] The degree of inhibition compared to controls was stated as 20–50%.[18]

Immunostimulant activity *In vivo* immunostimulant activity in mice (humoral and cellular), demonstrated by an enhancement of delayed hypersensitivity and antibody formation to sheep red blood cells, has been documented for the crude plant juice, Iscador and for a polysaccharide fraction isolated from the berries.[21] Activity was attributed to stimulation of the monophagocytic system and to induction of inflammation. The results indicated that the immunostimulant property of mistletoe is not solely attributable to the polysaccharides found in the berries (plant juice also active) or to the lactobacilli content of the fermented plant juice (crude extract also active). Non-specific immunological effects with mistletoe extracts are reported to be dependent on the frequency and quantity of the applied extract.[22]

Agglutinating activity Agglutinating activity that is preferential towards tumour cells over erythrocytes has been exhibited by Iscador and by a lectin fraction.[23–25] The lectins have been shown to bind to a number of cells including erythrocytes (non-specific to blood type),[7,10] lymphocytes, leukocytes, macrophages, glycoproteins and plasma proteins.[9,10] Binding has been found to be stereospecific towards units containing a D-galactose molecule,[8,9,25] although D-galactose units with unmodified hydroxyl groups at C_2, C_3 and C_4 inhibit erythrocyte agglutination.[26] Tyrosine residues are also thought to be involved in the agglutination process.[8] Plasma proteins compete for the lectin receptor site and, therefore, decrease the agglutination of erythrocytes and tumour cells.[27] Unlike many other sugars, lactose units have also been found to inhibit erythrocyte agglutination.[26]

Mistletoe lectins have been reported to prevent viscotoxin- and allergen-stimulated histamine release from human leukocytes.[28]

Hypotensive effect The hypotensive effect documented for mistletoe has been attributed to various biologically active constituents such as acetylcholine, histamine, gamma aminobutyric acid (GABA), tyramine and flavones.[G24] The exact nature of the hypotensive effect of mistletoe seems unclear: it has been reported that activity is mainly due to an inhibitory action on the excitability of the vasomotor centre in the medulla oblongata.[29] However, it has also been stated that the hypotensive action of mistletoe is mainly of a reflex character, exerting a normalising effect on both hypertensive and hypotensive states.[29] The effect of different mistletoe plant parts and host plant on the hypotensive activity has been studied with highest activity reported for mistletoe leaves parasitising on willow.[29]

Clinical studies

Iscador has been administered to patients with cancer of the breast, cervix, colon, rectum and stomach.[18] Treated groups were reported to show a slight

improvement over controls, the best results being obtained with cancer of the colon. It has been suggested that the relatively weak antitumour effects of Iscador may provide a useful adjunct to conventional surgery and radiotherapy.[18] Intrapleural instillation of Iscador has been used to dry out malignant pleural exudations[30,31] and it has been reported to increase lifespan in a fatal case of small-cell lung cancer.[32]

Cytolytic activity Cells responsible for natural killer (NK) cytolytic activity have been shown to be large granular lymphocytes (LGLs).[33] The cytolytic activity of NK cells is regulated by a number of factors including polymorphonuclear leukocytes (PMNs). A significant increase in NK cell cytotoxicity and antibody dependent cell-mediated cytotoxicity, with augmented concentrations of LGLs, has been noted in peripheral blood samples taken from breast cancer patients given a single infusion of Iscador.[34] A decrease in NK and LGL values has been shown to be paralleled by an increase in PMN concentrations in peripheral blood after Iscador infusion.[33] Interferons, interleukin 2 and some other lymphokines have previously been described as modifiers of the spontaneous cytotoxicity of NK cells and of monocytes.[35] The effect of Iscador on immunological parameters is stated to follow a kinetic pattern similar to that seen after treatment with interferon α.[34] Stimulation of cell-mediated immunity has been observed in female patients with arthrosis administered weekly injections (i.c.) of mistletoe extract.[22] A depressive action was observed in patients receiving daily administration of higher doses.[22]

Extracts of mistletoe have been shown to strongly increase the cytolytic activity of NK cells using human peripheral blood mononuclear cells and a human cell line (K562 leukaemia).[35] The active component in the mistletoe extract is stated not to be a protein, thus excluding lectins and viscotoxins, and is thought to be a complex polysaccharide.[35] Mistletoe extract is not itself cytolytic but must be present during the NK cell-mediated tumour cell lysis to elicit enhancement.[35] Galacturonic acid inhibits this enhancement of NK cell cytotoxicity by acting at the effector cell specific site.[35] Two mechanisms have been proposed for the enhancement of NK cell cytotoxicity by mistletoe; one involves a bridging mechanism between the effector (NK) and target (tumour) cells, and another involves an immediate trigger of receptor expression on effector cells for target cell recognition.[35]

A systematic review of controlled clinical trials of mistletoe extracts in the treatment of cancer identified 11 trials involving patients with various cancers (e.g. gastric, colorectal and cervical cancer).[36] Of these, ten trials reported results in favour of mistletoe treatment over control treatment, although most of these trials were deemed to be of poor methodological quality. The remaining, high-quality, trial reported no difference between the treatment and control groups.

Side-effects, Toxicity

Hepatitis has been documented in a woman who had ingested a herbal preparation containing kelp, motherwort, skullcap and mistletoe.[37] Mistletoe was assumed to be the causal factor since it was the only known toxic ingredient in the remedy.[37] However, no other instances of hepatotoxicity have been documented for mistletoe and, more recently, hepatitis has been documented with scullcap (*see* Scullcap).

Symptoms of toxicity documented following the ingestion of mistletoe include hypotension, coma, seizures, myosis, mydriasis and death.[38] Hypertension leading to cardiovascular collapse has been reported for American mistletoe (*Phoradendron* species).[38] It has been stated that no serious side-effects have been reported for Iscador following its administration to at least 1000 patients, although mild pyrexia and mild leukocytosis have been documented.[18] In contrast to the immunosuppression normally associated with cytotoxic therapy, Iscador has exhibited immunostimulant actions.

Toxic actions in animals have been documented for mistletoe lectins and viscotoxins.

Intravenous administration of viscotoxin to cats (35 μg/kg) resulted in a negative inotropic effect on cardiac muscle, reflex bradycardia and hypotension.[39] Viscotoxins A_3 and B have also caused muscle contracture and progressive depolarisation in isolated smooth, skeletal and cardiac muscle preparations (rabbit, frog).[40] The mode of action was thought to involve the displacement of calcium from cell membrane bound sites. The viscotoxins precipitate histamine release from human leucocytes in an irritant manner without destroying the cells.[28] Viscotoxin is toxic on parenteral administration and an LD_{50} value (mice, intraperitoneal injection) has been estimated as 0.7 mg/kg.[41]

Mistletoe lectins inhibit protein synthesis in both cells and cell-free systems.[42] In common with other known toxic lectins (e.g. ricin), mistletoe lectins bind to plasma proteins, are specific towards D-galactose, possess some cytotoxic activity and have caused macroscopic lesions in rats (e.g. ascites, congested intestine, pancreatic haemorrhages).[21] An LD_{50}

(mice) value for mistletoe lectin fraction is reported as 80 µg/kg compared with 3 µg/kg for ricin.[42]

Documented LD_{50} values (mice, intraperitoneal injection) are greater than 2.25 mg for the polysaccharide fraction from the berries, 32 mg for the crude plant juice, and 276 mg for Iscador.[21]

Contra-indications, Warnings

Mistletoe berries are highly poisonous and it is advised that the herb should only be prescribed by a registered herbal practitioner.[G42] Mistletoe may interfere with existing cardiac, immunosuppressant, hypo/hypertensive, antidepressant and anticoagulant/coagulant therapies.

Pregnancy and lactation The use of mistletoe is contra-indicated in view of the toxic constituents. Tyramine and a cardioactive principle isolated from mistletoe have both exhibited uterine stimulant activity in animal studies.

Pharmaceutical Comment

The constituents of mistletoe have been well investigated and to some extent are thought to be dependent on the host plant on which mistletoe is a parasite. Mistletoe is reputed to be a cardiac depressant. Cardioactive constituents are not generally recognised as constituents of mistletoe, although this may depend on the nature of the host plant.

Documented literature for mistletoe has centred primarily on the pharmacological and toxic actions of the lectin and viscotoxin constituents. Much interest has been generated by the immunostimulant and cytotoxic actions documented for mistletoe and its potential role in treating conditions involving the immune system. Mistletoe seems to have the unusual combination of being both cytotoxic and immunostimulating. Further research is required to establish the true usefulness of mistletoe in these therapeutic areas.

The toxic nature of the mistletoe constituents (e.g. alkaloids, lectins, viscotoxins) indicates that it is unsuitable for self-medication. Mistletoe berries may only be supplied from pharmacies.[43]

References

See also General References G2, G3, G5, G9, G10, G16, G22, G31, G36, G42, G43, G56 and G64.

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