Assessment of Extracts from Mistletoe (Viscum album) for Herb–Drug Interaction by Inhibition and Induction of Cytochrome P450 Activities

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Three commercially available extracts from mistletoe (Viscum album L.) grown on ash tree (abnobaVISCUM® Abietis 20 mg), on fir (abnobaVISCUM® Abietis 20 mg), and on pine (abnobaVISCUM® Pini 20 mg) were tested in vitro for their potential to interfere with the major drug metabolizing cytochromes P450 by hepatocyte viability, by inhibition of cytochromes P450 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4, and by the induction of cytochromes P450 1A2, 2B6, 2C9, 2E1 and 3A4. As the three extracts are produced from mistletoe plants belonging to three different subspecies of Viscum album L., they have explicit differences in the content and spectrum of various active ingredients, e.g., mistletoe specific lectins. Cytotoxic effects on liver cells were observed for abnobaVISCUM® Fraxini with a high lectin content with an EC50 value of 2.56 µg/mL, for abnobaVISCUM® Abietis with a moderate lectin content with an EC50 value of 5.79 µg/mL and for abnobaVISCUM® Pini with a low lectin content with an EC50 value of 30.86 µg/mL. The induction of cytochromes P450 was tested on human liver cells from three donors. Inhibition of cytochromes P450 was carried out on human liver microsomes. No or minor induction and inhibition was observed for all three extracts. The data indicate no or minor potential for herb–drug interactions by interference with cytochromes P450 by any of the three mistletoe extracts. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: mistletoe extract; herb–drug interaction; hepatocyte viability; cytochrome P450 inhibition; cytochrome P450 induction.

INTRODUCTION

Mistletoe extracts (Viscum album L.) have been prescribed frequently as complementary medicine in cancer therapy for more than 80 years (Kienle and Kiene, 2010), and are used often simultaneously with different chemotherapy treatments. As with any other herbal drug, there is awareness and a major concern for the possibility that pharmacokinetics and efficacy of these drugs is changed by inhibition or induction of cytochromes P450. A classic example is St John’s Wort, for which a dramatic change in the pharmacokinetic properties of various drugs by cytochrome P450 induction or inhibition has been described extensively in many different studies (Mathijssen et al., 2002).

The aim of this study was the assessment of the mistletoe preparations, abnobaVISCUM® Fraxini, abnobaVISCUM® Abietis and abnobaVISCUM® Pini for their potential to interfere with drug metabolism by the inhibition or induction of cytochromes P450 according to guidelines for in vitro screening of drug–drug interactions (EMEA, 1997; FDA, 2006; BfArM, 2004). These three preparations represent the three subspecies (ssp.) of Viscum album used for the production of the abnobaVISCUM drugs. Mistletoe from ash trees used for the abnobaVISCUM Fraxini preparation belongs to Viscum album L. ssp. Album. Mistletoe growing on fir trees belongs to the subspecies Viscum album L. ssp. Abietis. The mistletoe from the pine tree for the abnobaVISCUM Pini preparations belongs to the ssp. Austriacum. There are definite differences between the preparations of the three mistletoe subspecies in the content and spectrum of various active ingredients, e.g., lectins (Scheer et al., 1995). To detect any differences in cytotoxicity and of their metabolic interaction potential all three preparations were assessed.

MATERIALS AND METHODS

Mistletoe extract. The aqueous mistletoe extracts abnobaVISCUM® Abietis 20 mg, lot no. 712 B14; abnobaVISCUM® Fraxini 20 mg, lot no. 804 A28; and abnobaVISCUM® Pini 20 mg, lot no. 801B17; were obtained as commercially available solutions for injection from the manufacturer ABNOBA GmbH, Pforzheim, Germany. All three extracts are manufactured according to the German Homeopathic Pharmacopoeia (rule 32) as a pressed juice and contain 15 mg mistletoe extract from 20 mg mistletoe plant. 20 mg is the highest available concentration of the abnobaVISCUM extracts.

Human hepatocytes. Freshly plated human hepatocytes for induction studies from three donors (3 × 10⁵ cells per well in a 24-well plate, batch numbers: 23206-9706 (donor 1);
Human liver microsomes. Human liver microsomes were purchased from BD Biosciences, Woburn, USA, as pooled, mixed gender human liver microsomes, catalog no. 452156, lot nos. 18888, 28831, 88114 and 99268, and stored at -80°C until use.

Chemicals used in the MTT assay. InVitro Gro HI Medium cat. no. Z99009 Celsis InVitro GmbH, Neuss, Germany; penicillin/streptomycin cat. no. P11-010 PAA Laboratories GmbH, Pasching, Austria; dexamethasone cat. no. D9184 Sigma-Aldrich, Taufkirchen, Germany; MTT cat. no. A2231 AppliChem, Darmstadt, Germany; SDS cat. no. A2572 AppliChem, Darmstadt, Germany; N,N-dimethylformamide cat. no. A3725 AppliChem, Darmstadt, Germany; acetic acid cat. no. 49199 Fluka/Sigma-Aldrich, Taufkirchen, Germany; PBS cat. no. VX10010015 Invitrogen GmbH, Karlsruhe, Germany; ethanol cat. no. 1.00983 Merck, Darmstadt, Germany; sodium fluoride lot no. B481 Merck, Darmstadt, Germany.

Chemicals used in inhibition assays. Ammonium acetate, p.a., cat. no. 49638, Fluka, Sigma-Aldrich, Taufkirchen, Germany; MgCl₂, cat. no. 63063 Fluka, Buchs, Switzerland; potassium phosphate-buffer, 0.5 M, pH 7.4, cat. no. 451201, and β-NADPH tetrasodium salt, cat. no. A1395, BD Biosciences, Heidelberg, Germany; acetonitrile, cat. no. 01207802LC/MS AppliChem GmbH, Darmstadt, Germany; formic acid, ULC/MS, cat. no. 06914131, Darmstadt, Germany; penicillin/streptomycin, cat. no. P11-010 PAA Laboratories GmbH, Pasching, Austria; dexamethasone cat. no. D9184 Sigma-Aldrich, Taufkirchen, Germany; PBS cat. no. VX10010015 Invitrogen GmbH, Karlsruhe, Germany; ethanol cat. no. 1.00983 Merck, Darmstadt, Germany; sodium fluoride lot no. B481 Merck, Darmstadt, Germany.

Chemicals used in induction assays. InVitro Gro HI Medium, cat. no. Z99009 Celsis InVitro GmbH, Neuss, Germany; penicillin/streptomycin, cat. no. P11-010 PAA Laboratories GmbH, Pasching, Austria; dexamethasone, cat. no. D9184, DMSO, cat. no. 472301, salicylamide, cat. no. 86,041-7, and Krebs-Henseleit-buffer, cat. no. K3753 Sigma-Aldrich, Taufkirchen, Germany; ethanol, cat. no. 000983 Merck; acetonitrile, LC/MS cat. no. 01207802, formic acid, ULC/MS, cat. no. 06914131, and methanol, absolute LC/MS, cat. no. 13687082, and water, ULC/MS, cat. no. 23214125, Biosolve, Valkenswaard, Netherlands.

Chemicals used in growth assays. InVitro Gro HI Medium, cat. no. Z99009 Celsis InVitro GmbH, Neuss, Germany; penicillin/streptomycin, cat. no. P11-010 PAA Laboratories GmbH, Pasching, Austria; dexamethasone, cat. no. D9184, DMSO, cat. no. 472301, salicylamide, cat. no. 86,041-7, and Krebs-Henseleit-buffer, cat. no. K3753 Sigma-Aldrich, Taufkirchen, Germany; ethanol, cat. no. 000983 Merck; acetonitrile, LC/MS cat. no. 01207802, formic acid, ULC/MS, cat. no. 06914131, and methanol, absolute LC/MS, cat. no. 13687082, and water, ULC/MS, cat. no. 23214125, Biosolve, Valkenswaard, Netherlands; fetal calf serum, cat. no. 10270-106, InVitrogen GmbH, Karlsruhe, Germany.

Marker substrates, metabolites and internal standards. Phenacetin, content 99.4%, lot. no. S32704, Fluka; acetyaminophen, content 99.9%, lot. no. 115K0098, Sigma-Aldrich; acetaminophen-d₄, content 98.0%, lot. no. 8-SSR44-1, TRC; coumarin, content 100.0%, batch no. 056K1129, Sigma; 7OH-coumarin, content 98.7%, S34889, Aldrich; buproprion HCl, content 98.0%, lot. no. 31677-93-7, TRC; OH-buproprion, content 98.0%, lot. no. 00081, BD; OH-buproprion-d₆, content 98.0%, lot. no. 78308, BD; paclitaxel, content 99.2%, lot. no. HOG193 USP; 6α-OH-paclitaxel, content 98.0%, lot. no. 3-JQW-112-9, TRC; docetaxel, content 99.3%, lot. no. 1343815, Fluka; diclofenac sodium salt, content 99%, lot. no. 075K1896, Sigma; 4-OH-diclofenac-13C6, content 97%, lot. no. 17879, BD; S-mephenytoin, content 99.0%, lot. no. 2-RCD-56-4, TRC; 4-OH-mephenytoin, content 99.8%, lot. no. 065K3251, Sigma; 4-OH-mephenytoin-d₃, content 99.0%, lot. no. 065K3251, BD; bufuralol hydrochloride, content 97%, lot. no. 6-JWA-170-2, TRC; 1-OH-bufuralol maleate, content 99%, lot. no. 15537 BD; 1-OH-bufuralol-maleate-d₉, content 98%, lot. no. 18657, BD; chlorozoxazone, content 100%, lot. no. 102K1562, Sigma; OH-chlorozoxazone, content 97.0%, lot. no. 08778 BD; testosterone, content 99.4%, lot. no. 2099, Riedel de Haen; β-6OH-testosterone, content 99.0%, lot. no. 51730, BD; 6α-6OH-testosterone-d₉, content 99.0%, lot. no. 64732, BD.

Reference inhibitors. Furafylline, content: 99%, lot. no. 98451, BD; 8-methoxypsoralene, content: 100%, lot. no. 067K1469, Sigma; triethylenetriazinophosphoramid, content: 99.1%, lot. no. 107K1444, Sigma; quercetin, content: 99%, lot. no. 087K0744, Sigma; sulfaphenazole, content: 99%, lot. no. 056K1246, Sigma; omeprazole, content: 99.9%, lot. no. 086K1405, Sigma; quinidine, content: 87%, lot. no. 026K1021, Sigma; diethyldithiocarbamate, content: 101.2 %, lot. no. 1359427, Sigma; ketocazole, content: 99%, lot. no. 121H0524, Sigma.

Reference inducers. Rifampicin, content: 98%, lot. no. 087K1875, Sigma; omeprazole, content: 99.9%, lot. no. 086K1405, Sigma; phenobarbital, content: 100%, lot. no. EPP0900000, LGC; ethanol, content: 100%, lot. no. K38345783, Merck.

Cytotoxicity test procedures (MTT assay). The effect of the mistletoe preparations on hepatocyte viability was assessed in order to establish the maximum concentration of extract that could be tested without a direct cytotoxic effect. For this purpose, the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay was employed. Freshly plated male human hepatocytes, maintained in a CO₂ incubator at 37°C, 5% CO₂, and 95% humidity with a special liver cell adapted growth medium (InVitro Gro HI Medium, Celsis, Neuss, Germany), containing 1% (v/v) penicillin/streptomycin and 0.05% (v/v) dexamethasone stock solution (100 µM dexamethasone in ethanol), were exposed in 96-well microtiter plates with 10⁵ cells per well to mistletoe preparations in a concentration range of 0.002–2000 µg/mL final concentration in 100 µL growth medium for 48 h, with exchange of growth medium after 24 h. Control by microscope showed no precipitations in the incubations, except for the incubations with a concentration of 2000 µg/mL. All concentrations of the test items were tested as 8-fold replicates. Incubation was changed against MTT working solution for 1.5 h. The MTT working solution was 2.5 mL stock solution (5 mg/mL in PBS) + 7.5 mL hepatocyte incubation medium. Conversion of the tetrazolium salt (MTT) to formazan by viable cells was measured photometrically at 570 nm after lysis of the cells by shaking in lysis buffer. Lysis buffer was 39% (v/v) water, 39% (v/v) dimethylformamide, 2% (v/v) acetic acid, 20% (w/v) SDS. The cell viability was measured as percentage of the signal from the negative control without test item. Sodium fluoride at a concentration of 250 µg/mL served as a positive control.

Cytochrome P450 inhibition. The mistletoe preparations were tested at concentrations of 0.2, 2.0 and 200 µg/mL with pooled human liver microsomes (0.5 mg microsomal protein/mL) in 10 mM potassium phosphate buffer, pH 7.4 for effects on CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 activities by specific
marker reactions in the presence of 3 mM magnesium chloride, and 2 mM NADPH in a 96-well microtitre plate at 37 ± 0.5 °C. All incubations were performed in triplicate. The total volume of the individual incubation was 240 μL. The marker substrate concentrations in the incubation mixtures were chosen at concentrations close to their apparent Km. Mistletoe extract or CYP specific inhibitor were preincubated with a microsomal suspension for 5–10 min, and the incubations were started by the addition of the respective marker substrate. The incubation was stopped after 30 ± 1 min, as the formation rate of all investigated metabolites was linear with time up to 30 min, by pipetting 200 μL incubation mixture into a vial containing 200 μL ice-cold acetonitrile as the stop reagent. The samples were centrifuged for 10 min at 4 °C at 3000 × g, and the supernatant was transferred to a new 96-well microtiter plate for tandem HPLC-mass spectroscopy to analyse and measure the remaining marker substrates and resulting metabolites. Samples spiked with marker substrates and marker metabolites were used for calibration curves in order to quantify substrates and metabolites. Incubation samples containing no test item and no CYP specific inhibitor but identical concentrations of the corresponding solvent type of the test item incubations served as negative controls of inhibition (NC). Incubation samples containing the CYP specific inhibitor served as positive controls (PC) for inhibition. The final concentrations of the marker substrate in the individual incubation medium were as follows: 2 mM phenacetin for CYP1A2; 2 mM coumarin for CYP2A6; 40 mM bupropion for CYP2B6; 4 mM paclitaxel for CYP2C8; 4 mM diclofenac for CYP2C9; 20 mM S-mephenytoin for CYP2C19; 8 mM bufluralin for CYP2D6; 2 mM chlorozoxazine for CYP2E1; 40 mM testosterone for CYP3A4. The measured metabolites were acetaminophen for CYP1A2; umbelliferone for CYP2A6; hydroxybupropion for CYP2B6; 6β-hydroxy-paclitaxel for CYP2C9, 4′-hydroxy- diclofenac for CYP2C9, 4′-hydroxymephenytoin for CYP2C19, hydroxybupropion for CYP2C9, 6′-hydroxyclochloroxazine for CYP2E1, and 6β-hydroxytestosterone for CYP3A4. The concentrations of the CYP specific inhibitors in the incubation samples were as follows: 10 μM furafylline for CYP1A2; 0.3 μM 8-methoxysporalen for CYP2A6; 30 μM triethylenemetaphosphamide for CYP2B6; 1 mM quercetin for CYP2C8; 0.8 μM sulfaphenazole for CYP2C9; 3 mM omeprazole for CYP2C19; 120 μM quinidine for CYP2D6; 1.2 mM diethylthiocarbamic acid sodium salt for CYP2E1; 60 μM ketoconazole for CYP3A4 (FDA, 2006).

Cytochrome P450 induction. The mistletoe preparations were tested for CYP induction with freshly isolated human primary hepatocytes from three individual donors. Hepatocytes were seeded in 24-well plates at a cell concentration of 3 × 10^5 per well. The three mistletoe preparations were prepared at concentrations of 0.2, 2.0 and 4.0 μg/mL. The induction potential of the different extracts on CYP isoenzymes 1A2, 2B6, 2C9, 2E1 and 3A4 was measured by the respective marker substrate as described above for CYP inhibition in comparison with reference inducers. Incubations containing reference inducers for CYP1A2 (omeprazole, 50 μM), CYP2B6 (phenobarbital, 1 mM), CYP2C9 (rifampicin, 10 μM), CYP2E1 (ethanol, 100 mM) and CYP3A4 (rifampicin, 10 μM), respectively, served as reference induction controls. Three replicates per reference control were tested. Following 48 h equilibration of the hepatocytes at 37 °C in hepatocyte growth medium, the mistletoe preparations and reference inducers were added to the hepatocytes over a period of 72 h with renewal of medium and test reagents every 24 h. The 72 h induction period was followed by a 3 h incubation of the hepatocytes with the marker substrates. The reactions were terminated by taking the supernatant, and mixing with an equal volume of ice-cold acetonitrile, followed by centrifugation for protein precipitation at 4 °C. The resulting supernatant was submitted to tandem HPLC-mass spectroscopy for the detection and measurement of metabolites.

Tandem HPLC-mass spectroscopy. Separation and detection of marker substrates and marker metabolites was achieved with HPLC (Waters Alliance 2705, Eschborn, Germany) and mass spectroscopy (Quatro LC, Micromass, Wythenshawe, UK) on a C18 column (Symmetry, 3.5 μm, 46 × 7 mm, Waters, Eschborn, Germany) with a C18-precolumn (Phenomenex, 4 × 3 mm, Aschaffenburg, Germany). HPLC parameters are shown in Table 1, MS parameters in Table 2.

Analyses of data and acceptance criteria of MTT assay. The mean of n replicates was calculated using the Excel function ‘mean’. The blank was subtracted from the means of the samples before further calculation. The SEM (standard error of mean), % compared with the negative control, and SE (standard error) were calculated as described below using the respective Excel functions. A cytotoxic potential of a test item in the tested range is assumed if (i) a decrease of vital cells over the spread is observed (at least 20% decrease of OD_{570} compared with the negative control), (ii) a dose-effect relationship is observed (if one concentration shows a 20% decrease of OD_{570}, all higher concentrations should show a higher decrease of OD_{570}). The test is considered as valid if (i) the positive control produces a decrease of vital cells relative to the negative control (≤50%), (ii) The mean OD_{570} of the negative control minus blank is at least 0.1.

Analyses of data and acceptance criteria of CYP induction. Data analysis of the CYP induction experiments was performed using standard software: ‘MS-EXCEL™ 2002’ by Microsoft, Inc., ‘MassLynxTM Vers. 4.0’ and ‘QuanLynxTM’ by Micromass, Ltd. The mean of n replicates was calculated using the Excel function ‘mean’. The SEM (standard error of mean), % compared with the negative control, and SE (standard error) were calculated using the respective Excel functions.

Analyses of data and acceptance criteria of CYP inhibition. Analysis of samples from CYP inhibition experiments were accepted, when the following criteria were met:

(i) positive controls showed an inhibition of CYP of at least 30% compared with the negative control; (ii) a minimum of six back-calculated calibration standards have to fall within ±15%, except for the calibration standard at the LLOQ, which has to be within ±20% of the nominal value; (iii) at least 2/3 of the QC samples have to be within ±15% of their respective nominal value. 1/3 of the QC samples can be outside ±15%, but not all replicates at the same concentration level. Data analysis of the CYP inhibition experiments was
performed using standard software: ‘MS-EXCEL 2002™’ by Microsoft, Inc., ‘MassLytxTM Vers. 4.0’ and ‘QuanLynxTM’ by Micromass, Ltd.

The mean of \( n \) replicates was calculated using the Excel function ‘mean’. The SEM (standard error of mean), relative SEM, % compared with the negative control, and SE (standard error) were calculated as described below using the respective Excel functions. The obtained inhibition rates were classified according to FDA (2006) as follows: no/minor inhibition: <25% inhibition; intermediate inhibition: ≥25% and <50% inhibition; major inhibition: ≥50% inhibition.

**RESULTS**

The hepatocyte viability differed for the three mistletoe preparations, with abnobaVISCUM® Fraxini starting to exert cytotoxic effects at 0.2 µg/mL, abnobaVISCUM® Abietis starting at 2 µg/mL and abnobaVISCUM® Pini starting at 30 µg/mL. A dose-dependent cytotoxic effect was observed for all three mistletoe preparations, with EC\(_{50}\) values for abnobaVISCUM® Fraxini of 2.56 µg/mL, for abnobaVISCUM® Abietis of 5.79 µg/mL and for abnobaVISCUM® Pini of 30.86 µg/mL (Fig. 1 A, B, C). Precipitates were observed in all cell incubations at the concentration of 2000 µg/mL. Therefore, this value was omitted from the curve fitting.

For the nine major drug metabolizing cytochromes P450, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4, no or minor inhibition was observed for all three mistletoe preparations. Particularly, no dose related effects were found. Inhibitory effects (values above 0%) of the three abnobaVISCUM® are shown in Fig. 2 A, B, and C.

**DISCUSSION**

The studies represent a screening in vitro investigation of the potential of the commercially available proprietary mistletoe extracts abnobaVISCUM® Fraxini 20 mg, abnobaVISCUM® Abietis 20 mg and abnobaVISCUM® Pini 20 mg to interact with cytochrome P450 mediated metabolism.

Hepatocyte viability studies with all three mistletoe preparations were performed in order to ensure a viability rate of at least 80% in the CYP induction studies with intact liver cells (Fig. 1 A, B, C). Interestingly, the toxicity of all three mistletoe preparations differed, and
may be related to the different content of lectins in the three mistletoe preparations. The highest toxic effect was
observed with abnobaVISCUM® Fraxini with an EC$_{50}$ value of 2.56 µg/mL and a lectin concentration of 16.19 µg/mL in this batch tested, whereas abnobaVIS-
CUM® Abietis had an EC$_{50}$ value of 5.79 µg/mL and a
ductin concentration of 2.5 µg/mL and abnobaVIS-
CUM® Pini with an EC$_{50}$ value of 30.86 µg/mL had
the lowest concentration of lectins with 0.8 µg/mL. This
confirms an earlier observation by Scheer et al. (1995),
who reported a low toxicity of mistletoe preparations
from mistletoe grown on pine, due to their low lectin
concentrations.

Three concentrations (4, 2 and 0.2 µg/mL) were
chosen for the cytochrome P450 induction studies at
which at least 80% viability of the liver cells was given.

A pharmacokinetic study conducted with a single
subcutaneous dose of abnobaVISCUM® Fraxini 20 mg
(Huber et al., 2010) yielded a C$_{max}$ range of 3.738 ng/mL
and 0.1887 ng/mL for the mistletoe lectins. This

Figure 1. Cytotoxic effects of abnovaVISCUM on human hepato-
cytes. Fraxini (A), Abietis (B), Pini (C).

Figure 2. Inhibitory effect of abnobaVISCUM Fraxini (A), abnoba-
VISCUM Abietis (B), and abnobaVISCUM Pini(C) on the metabolic
activity of nine major human hepatic cytochromes P450 at 200 µg/ml
(first bar), 2.0 µg/ml (second bar), and 0.2 µg/ml (third bar).
corresponds to a maximum of 56% bioavailability of the lectins in the serum 1 h after subcutaneous injection. If it is assumed that the bioavailability of the whole mistletoe extract (which is impossible to measure as it is a multicomponent mixture) is comparable to the lectins, a maximum serum level of 1.04 µg/mL. Therefore it can be estimated at around 3.7 µg/mL with an average concentration (200 µg/mL) inhibition rates between 20% and 25% were the highest measured in the present investigation. An inhibition rate up to 25% is still regarded as no/minor inhibition and has no significant relevance regarding interactions with other drugs, especially as it was not dose-dependent. This is in contrast to Engdal and Nilsen (2009) who reported an inhibition of cytochrome P450 3A4 with another mistletoe preparation at concentrations beyond 100 µg/mL. However, this inhibition was judged too weak to account for clinical relevance. In our investigation the concentration of 200 µg/mL showed no relevant cytochrome P450 3A4 inhibition. This might be explained by the different extraction and manufacturing process. The extract used in the investigation of Engdal and Nilsen (2009) is manufactured with an additional fermentation step after the water extraction.

Overall, regarding the cytochrome P450 inhibition and cytochrome P450 induction rates by all three extraction rates indicate no interaction potential on the cytochrome P450 enzyme system, although the content of pharmacologically active ingredients such as lectins varies by a factor of > 20. It is therefore likely that no clinically significant interactions occur for any of the three extracts. These preclinical findings were confirmed by a clinical investigation with another mistletoe extract. Mansky et al. (2005) reported on a phase 1 study investigating the influence of an additional mistletoe therapy on the plasma concentration of the cytostatic was unaffected by different doses of the additionally applied mistletoe therapy.

Acknowledgements

All studies were funded by ABNOBA GmbH, Hohenzollernstraße 16, Pforzheim, Germany. However, the experiments were designed and carried out independently by BioProof AG, without influence of the sponsor, and observing GLP regulations.

Conflict of Interest

The authors have declared that there is no conflict of interest.
REFERENCES


