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Adjuvant Cancer Biotherapy by *Viscum Album* Extract Isorel: Overview of Evidence Based Medicine Findings

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ABSTRACT

*Within the integrative medicine one of the most frequently used adjuvant cancer biotherapies is based on aqueous mistletoe (*Viscum album*) extracts. Tumor growth inhibition, stimulation of host immune response and improvement of the quality of life are the positive effects of mistletoe therapy described in several preclinical and clinical studies. However, cumulative results of the evidence based medicine findings on such treatments are rarely given. Therefore, this paper evaluates the evidence based findings describing effects of the Viscum album extract Isorel in cancer therapy with respect to the type of therapy, stage and type of illness. This study presents cumulated data for 74 patients with different types and stages of cancer treated by Viscum album extract as adjuvant treatment to different conventional therapies, mostly combined surgery and radiotherapy. The biotherapy effectiveness was evaluated according to the outcome as 1) no major therapeutic improvement (15% of patients), 2) prevention of tumor recurrence (47% of patients) and 3) regression of cancer (38% of patients). Notably, there was no obvious health worsening during the follow up period at all. Thus, the results obtained for conventional anticancer therapies combined with adjuvant biotherapy based on Viscum album extract seem to be beneficial for the majority of cancer patients (85%) without serious side effects.*

Key words: Viscum album*, cancer, biotherapy, mistletoe, lectins, evidence based medicine*

Introduction

Mistletoe (*Viscum album*) has a long history as plant source for the preparation of different extracts used for therapy of cancer[1–7]. Namely, numerous data point to a cytotoxic action of these extracts against different tumor cell lines, while their *in vitro* toxicity for the normal, or at least less malignant, cells is less pronounced, indicating relatively selective toxicity primarily against the tumor cells[8–14]. On the other hand, the application of the *Viscum album* extracts *in vivo* might have immunomodulating effects, mainly stimulating cytotoxic activity of lymphocytes[12,13,15,16]. The dual activity of the mistletoe preparations, i.e. cytotoxicity for the tumor cells and enhancement of the immune host defense against the malignant cells, gives support for the practical use of the preparations in human medicine. Mistletoe lectins (ML) I, II and III (complex proteins of high molecular weight 30–120kDa) are believed to be the active component of mistletoe extracts, since they achieve a prominent cytotoxic effect in low concentrations and are consequently the best investigated components of mistletoe extracts[17,18]. Still, lectins are not the only active substances in aqueous mistletoe extracts[19]. Biologically active substances, such as viscotoxins, flavonoids, oligosaccharides, alkaloids, lipids, phytosterols, triterpens, and several enzymes are also present causing the increase in overall activity of the extract compared to the pure lectins[17,18]. Nowadays, viscotoxins are cloned in *Escherichia coli* making them accessible for possible application in cancer therapy[20].

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Initial clinical trials were promising, therefore, currently prospectively randomized multicentre trials are being performed to evaluate the ability of complementary ML–1 treatment to reduce the rate of tumor recurrences and metastases, to improve the overall survival as well as the quality of life and to exert immunoprotection in cancer patients under tumor destructive therapies[21–23]. These findings are in agreement with previous clinical studies that indicated usefulness of various *Viscum album* extracts in the therapy of cancer[24]. However, in such studies it is often difficult to compare results obtained using different types of plant extracts for therapy of different types of cancer at different stages of illness. We have described previously that a tetrazolium salt based colorimetric assay (MTT) is applicable as *in vitro* assay for the analysis of the batch consistency of one of registered *Viscum album* aqueous extracts, namely the drug Isorel[25] (Vysorel®). Hence, it was found that the biological activity of the drug could be considered as standardized if compared to the activity of the purified ML–1. Taken together, the anticancer effect of the extract was proven in various *in vitro* and *in vivo* experimental models[11,13] with clinical trials showing its beneficial effects in the therapy of cancer patients[21,22]. The aim of this study was to summarize evidence based findings on Isorel anticancer activity using the current approach of evidence based medicine (EBM) in discussion of the findings[26].

Materials and Methods

Viscum album extract

A preparation of the fresh plant aqueous extract (Novipharm GmbH, Austria) was used s.c., i.m. and i.v. according to the recommended, registered producer's protocols and physicians' expertise of their patients. The *Viscum album* extract Isorel is produced under GMP standards by cold extraction of the entire plant in saline, without homogenization of the plant or extract fermentation. It contains several active substances: mistletoe lectines, viscotoxines, flavonoides, polysaccharides, triterpenes, etc. However, it should be mentioned that the plain drug is a more effective tumoricidal agent than any of its active components alone showing adjuvant therapeutic efficacy of the bioactive mistletoe components[27]. Moreover, the overall anticancer effects of the drug show very good batch consistency, as verified by standardised bioassay on several cell lines, and resemble anticancer effects of the purified mistletoe lectines (ML–1)[25].

On the other hand, relative proportions of the plant extract components differ not only regarding to the mistletoe host–trees and seasonal variations of different years, but also regarding the respective time of harvest. Therefore, quantitative specifications can be made only in a wide concentration range for each substance, while the flavonoids are the lead substance from point of view of quality control. According to the European Pharmacopoeia (2.2.27) a validated qualitative identification of the different Isorel–preparations (A, M, P) is possible through distinct fingerprints obtained by thin layer chromatography (TLC). Namely, Isorel and a reference solution of flavonoids are applied on a stationary phase (silica gel on aluminum foil) and are together with the mobile phase (a mixture of ethyl acetate, ethylmethylketone, formic acid and water) drawn up the silica gel plate via capillary action. Consequently separation of flavonoids is achieved, because of their different mobility in TLC (Fig. 1, courtesy of Novipharm GmbH).

Thus, the GMP produced and by bioassay validated, according to the flavonoid content standardised types of Isorel prepared from the fir tree mistletoe – *Abies* (A), apple tree – *Mali* (M) and pine tree – *Pini* (P) were used. Selection of the type of drug applied depending on the type of the host tree is based on the practical experience of medical doctors obtained over decades of practical work, as in case of other mistletoe drugs. They all followed manufacturer's recommendations and complied with them. Upon request the Isorel manufacturer (www.novipharm.at/english/home.html) provides any other needed information both to the medical practitioners as well as to the patients. All patients were receiving Isorel according to the guidelines for this complementary biotherapy. Therefore, they were treated every second day for three times a week during the first year after cancer diagnosis, while in case of can-

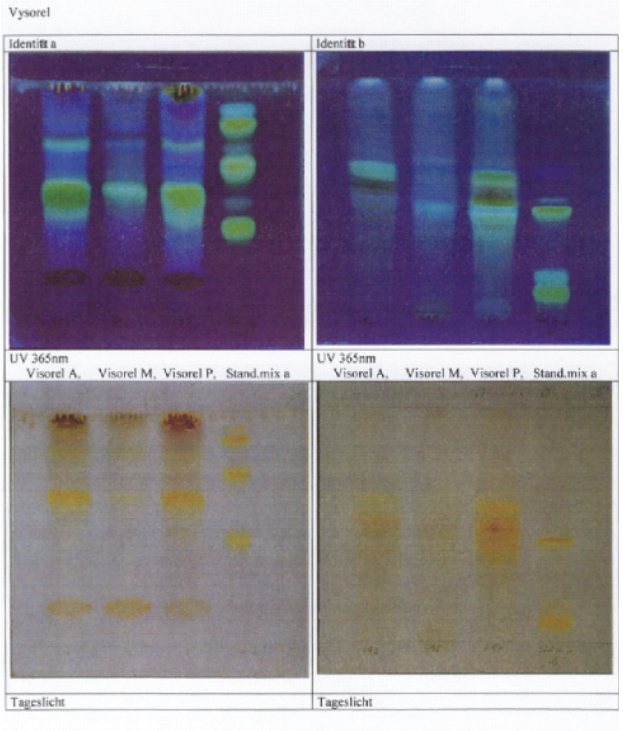

Fig. 1. TLC-fingerprint of Isorel® (=Vysorel®) A, M and P Strength 60 The thin-layer chromatography analyses based on Pharm. Eur., monograph Birch Leaf (7.0/1174) conforms to respective authentic reference sample revealing the content of flavonoids in Isorel as A: 16-35 µg/ml, M: 5-18 µg/ml and P: 28-65 µg/ml respectively.

cer remission the treatment was after first year reduced to one per week and was maintained in such a way afterwards. In case of chemotherapy or radiotherapy, Isorel was used between the cycles of these treatments, while in case of surgery Isorel was introduced from convalescence further. The patients did not have to pay for Isorel therapy, since it was covered by the health insurance funds.

Patients

Documentation in form of brief case reports was obtained for 45 patients provided by the drug producer Novipharm, while the other 29 cases were evaluated on the basis of the published case reports. Thus, in total there were 74 case reports analysed for 46 female and 28 male patients aged from 26–88 years (average 57) monitored for different time intervals (4 to 156 months, on average 31,8) as shown in Table 1. The overall duration of the therapy with Isorel was individually determined, since the monitoring period was also different for different patients, as reported by their doctors who provided the evidence base data analysed. All the patients were using Isorel continuously following the guidelines of the pharmaceutical company Novipharm relaying also on the positive experience of the doctors. The documentation received could be considered as case reports in which staging of the malignant disease was done in respective clinics where patients were diagnosed and treated initially (by surgery, chemo– and radio–therapy) that relied on the TNM classification. There were no particular additional diseases noticed which could be considered of major relevance for the efficiency of the therapy during the time studied (except pneumonia in one case and diabetes in the other, but in both cases of uncertain relevance for the therapy applied).

Distribution of patients according to type of cancer

Patients included in the study were suffering form different types of cancer localized in almost all organic systems (Fig. 2). Mostly they had mammary carcinoma (N=21) or carcinoma developed in the digestive system (N=21) in almost each possible location (in particular colon and rectum).

Patients were initially divided into three groups (Fig. 3). The first group denoted as "initial" (N=25) were patients with tumors in an early stage of development, with the assumption the cancer did not have any manifested metastases. The second and third groups were denoted

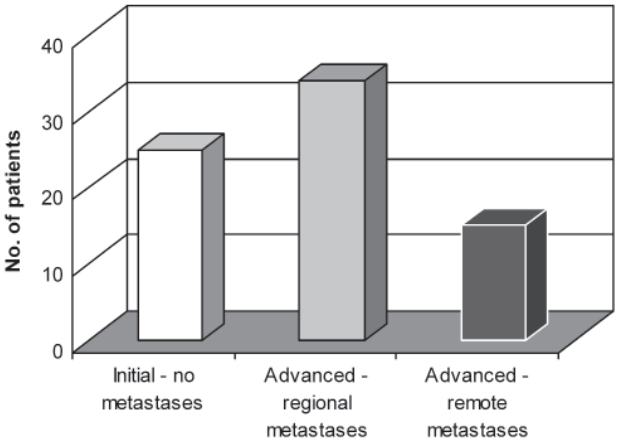

Fig. 3. Classification of patients by the stage of tumor development. Patients were distributed in 3 groups denoted as initial – without metastases; advanced – with local metastases; advanced – with remote metastases in other organs.

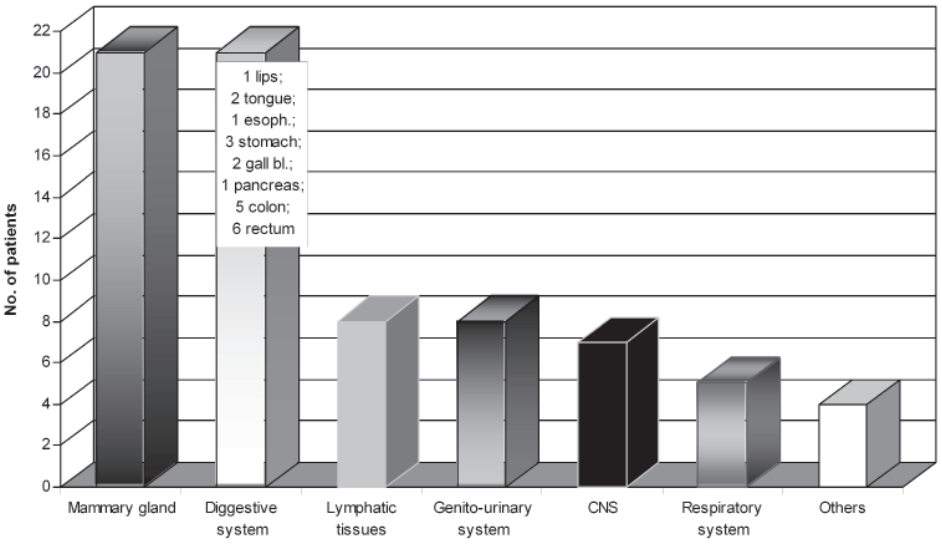

Fig.2. Classification of patients by cancer localization/type. Mammary carcinoma and digestive tract carcinoma were the most common.

TABLE 1
DISTRIBUTION OF PATIENTS ACCORDING TO THE AGE, SEX AND TIME MONITORED

	Male	Female	Total
Number of patients	28	46	74
Age range	26–88	33–85	26–88
Mean	58.17	56.30	57.22
	Follow up	(month)	
	Male	Female	Total
Range	4–144	6–156	4–156
$\overline{X}$	33.14	30.86	31.79

"advanced" with difference in severity, namely, second group (N=34) consisted of patients with advanced cancer without or with only local metastases, unlike the third group (N=15) which had remote metastases in other organs.

Distribution of patients according to therapy applied

As can be seen from Fig. 4, there were only 12 patients who were treated by Isorel solely (one patient received initially for one week another *Viscum album*, extract – Iscador®, which was replaced by Isorel afterwards for six years), while the other patients received Isorel after or in parallel to the applied therapeutic protocols. Most of the patients (N=36) received Isorel combined with radiotherapy and/or chemotherapy, which were applied for 27 patients after surgery, while 9 patients were not surgically treated. There were 26 patients treated with Isorel after surgery (removal of cancer and, desirably, some local lymph nodes) who did not receive radiotherapy or chemotherapy. One patient was for the initial period of one week receiving another type of the mistletoe extract, which was replaced by Isorel afterwards for the consecutive period of six years.

Statistics

The results obtained were evaluated using Chi–square test to define distribution of the patients according to the outcome in dependence on the type of cancer, stage of disease and therapies applied.

Results

Therapeutic efficiency – general findings

Most of the patients (35/74 – 47%) did not have signs of tumor recurrence and/or metastases developed, at least during the time monitored (Figure 5). The incidence of these patients in comparison to those that showed no major improvement (N=11, 15%) or oppositely signs of tumor regression (N=28, 38%) was significantly (p=0.0006) higher. There were no patients at all with signs of severe worsening of the health due to the cancer progression. Thus, from this study it could be concluded that the major therapeutic effects of Isorel therapy alone or combined with conventional therapy is prevention of the tumor recurrence and/or prevention of development of metastases.

Therapeutic efficiency – dependence on the stage of illness

The stage of illness did not strongly influence the efficiency of the therapies applied (see Table 2). For the pa-

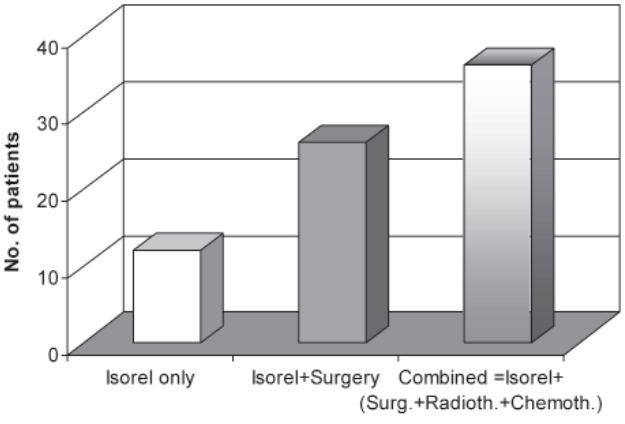

Fig. 4. Classification of patients by therapy received. Only 12 patients received solely Isorel, 26 were treated with Isorel after surgery and 36 were treated with Isorel in combination with surgery and/or radiotherapy with or without chemotherapy.

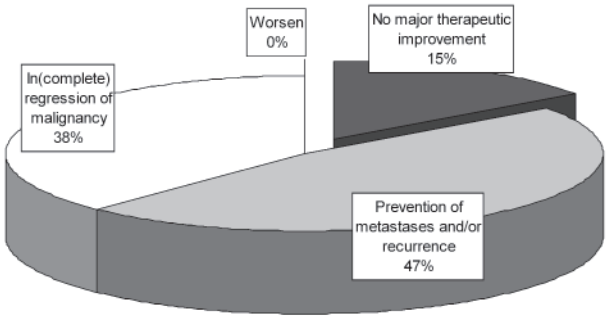

Fig. 5. The effects of Isorel therapy. The majority of patients (47%) did not exhibit have tumor recurrence in the follow up period, 38% of patients showed had incomplete regression, and 15% did not have any improvement. There were no patients with severe worsening of the health due to cancer progression.

TABLE 2
THE EFFECTS OF CANCER THERAPIES APPLIED ACCORDING TO THE STAGE OF ILLNESS

	OUTCOME (during the period monitored [4 to 156 months])			
Stage of illness	No major therapeutic improvement	Prevention of metastases and/or recurrence	(In)complete regression of primary tumor ± prevention of metastases and/or recurrence	Total
Initial – no metastases	1	20	4	25
Advanced – regional metastases	6	13	15	34
Advanced – remote metastases	4	2	9	15
Total	11	35	28	74

tients with initial phase of cancer the most common finding of the outcome was prevention of the tumor recurrence and/or prevention of development of metastases ($p<0.0001$). The group of patients with advanced cancer mostly associated with regional metastases (N=34), did not show the same results. Namely, there was no prevalence of a particular outcome in these patients ($p=0.138$). However, if patients with the most favorable outcome (partial or complete regression of primary tumor and/or metastases) were combined with the group of patients whose outcome was defined as "prevention of development of metastases and/or cancer recurrence", the total incidence of these patients was 82%, versus 18% that showed only improved general health condition ($p=0.0002$). Further, patients suffering from the most advanced cancer associated with remote metastases (N=15) did not have any principal anticancer effects of applied therapy ($p=0.0743$). Namely, only in 13% patients the therapies applied showed effects of prevention of the tumor recurrence and/or prevention of metastases development, while in 27% patients no major improvement was observed (except improved general quality of life, such as appetite, activity, etc.). In the group of patients with the most advanced illness there were also 60% patients who showed favorable results of the therapy that could be defined as regression of the primary tumor as well as prevention of the tumor recurrence or metastases, at least during the period monitored. In spite of that, combining the two beneficial outcomes (prevention of tumor recurrence and (in)complete regression of tumor and/or metastases; N=11) and comparing it to those with only palliative improvement of general well being (N=4) did not give a significant difference ($p=0.0703$) for patients with the most advanced cancer.

Dependence of the outcome on the type of therapy

As can be seen from Table 3, the most common outcome ($p=0.0006$) was prevention of tumor recurrence and/or prevention of metastases development (N=36) which was the significantly dominant outcome in patients treated with combined therapies ($p=0.0488$) and for patients receiving Isorel after surgery ($p=0.0001$). Such a distribution was not noticed for patients receiving Isorel solely, since there was only one patient in this group with such outcome. Therefore, the highest incidence was in the group of patients showing signs of tumor regression ($p=0.0087$).

A positive impact of radiotherapy and chemotherapy was noticed in comparison to the patients with therapy consisting only of surgery and Isorel. Namely, if the patients receiving combined therapies (N=36) were compared with those receiving only surgery and Isorel (N=26), the incidence of the outcome defined as "prevention of tumor recurrence or metastases", significantly decreased (from 73% to 44%) in favor of the most desired effects defined as "regression of the tumor and prevention of tumor recurrence or metastases" that increased from 15% to 42% ($p=0.0097$).

TABLE 3
THE EFFECTS OF CANCER THERAPIES APPLIED ACCORDING TO THE TYPE OF THERAPY USED

	OUTCOME (during the period monitored [4 to 156 months])			
type of therapy	No major therapeutic improvement	Prevention of metastases and/or recurrence	(In)complete regression of primary tumor ± prevention of metastases and/or recurrence	Total
Isorel only	2	1	9	12
Isorel + surgery	4	18	4	26
Combined = Isorel + surg.± radioth.± chemoth.	5	16	15	36
Total	11	35	28	74

Dependence of the effects of therapies on the type of cancer

Because the outcome of different cancers is often different due to their sensitivity to similar kinds of therapy, for the evaluation of the data available, the patients were further separated into three major subgroups denoted as: 1) patients with mammary carcinoma (N=21); 2) patients with gut cancer (colon or rectum carcinoma) (N=11) and 3) patients with other types of cancer (including lymphoma/leukemia, carcinoma of pancreas and gall bladder, bronchial and thyroid cancer, various malignancies of CNS, as well as Schwanoma, liposarcoma, prostatic cancer, ovarian carcinomas, in total N=42). The findings of the influence of type of cancer on the outcome are presented in Table 4.

For all three groups of patients beneficial effects of therapies (combined "prevention of tumor recurrence and/or metastases development" and "(in)complete regression of cancer") were much more pronounced compared to improved quality of life only, denoted as "no major therapeutic improvement" (for all the groups and total, $p<0.01$). While for patients with colon cancer the major beneficial outcome was prevention of tumor recurrence (82%) due to the early cancer diagnosis and therapy applied at the initial stage (see Table 1), for the other two subgroups (mammary carcinoma versus all other types of cancer) the same distribution of the effectiveness of therapies was observed ($p=0.2381$). For these two subgroups "prevention of tumor recurrence or metastases development" gave the same incidence as "(in)complete regression" (for mammary carcinoma, $p=0.4913$; for other cancers, $p=0.3778$) thus indicating that the type of cancer was not as relevant a parameter for the determination of effects of therapies applied as was the stage of illness.

Discussion

Aqueous mistletoe extracts are used by a large number of cancer patients, and more and more studies confirm its beneficial effects on various type of cancer[14,21,28]. Evidence gained over the last two decades has classified the mistletoe extract therapy as one of the most attractive approaches in adjuvant cancer therapy, as acknowledged by the National Institute of Health, although these drugs are not yet registered by the Food and Drug Administration in the USA (www.cancer.gov/cancertopics/pdq/cam/mistletoe/HealthProfessional). Still, there are some inconsistent conclusions from some clinical trials, mainly due to different types of drugs and protocols used[24,29].

Mistletoe extracts showed dual activity in tumor patients, exerting cytotoxicity against tumor cell on the one hand and immunomodulating effects on the other. Various authors report selective cytotoxicity against different tumor cell lines, with no pronounced toxicity against non malignant cell lines[13,30,31]. Immunomodulating effects of mistletoe extracts are of value in cancer therapy because combined immuno depressive effects of cancer and surgery may augment the risk of postoperative infections and dissemination of malignancy, leading to the reduction of overall recovery and quality of life. Most of the studies showed beneficial effects of different mistletoe extracts in patients with certain cancer types[14,21] but there are not enough correlation data of the mistletoe therapy and its outcome in tumor patients grouped on different bases. Therefore, here we evaluate the therapeutic effect of the mistletoe extract Isorel on several different bases: stage of illness, type of therapy and type of illness.

For the evaluation of the effects of mistletoe extracts we have used the drug Isorel, a total aqueous extract of mistletoe. Previous studies endorsed Isorel as immunomodulating agent with cytotoxic effect toward malignant cells thereby increasing the efficiency of radio– and chemotherapy[3,6]. Most studies showed a perspective in combined chemotherapy and Isorel biotherapy[6,25,32]. Our study showed that biotherapy with Isorel had positive effects, with the most common outcome favorable for patients causing prevention of tumor recurrence and prevention of metastases. Encouragingly, there was no severe worsening of health due to cancer progression. Especially effective was the combination of radio– and/or chemotherapy with or without surgery and Isorel biotherapy. Namely, the combination of therapies gave two favorable outcomes indicating the importance of adjuvant therapy in treating the cancer.

The stage if illness is especially important in cancer treatment as early detection of tumor increases the chances of recovery. Indeed, if Isorel is used as adjuvant therapy

TABLE 4
THE EFFECTS OF CANCER THERAPIES APPLIED ACCORDING TO THE TYPE CANCER

	OUTCOME (during the period monitored [4 to 156 months])			
Type of cancer	No major therapeutic improvement	Prevention of metastases and/or recurrence	(In)complete regression of primary tumor ± prevention of metastases and/or recurrence	Total
Mammary carcinoma	2	11	8	21
Colon + rectum carcinoma	1	9	1	11
Other	8	15	19	42
Total	11	35	28	74

in an initial stage of the illness the chances for a positive outcome of the therapy are high. The progression of the illness shift this result to (in)complete regression of primary tumor and prevention of metastases, with no statistical difference between positive outcome and "no improvement" outcome in an advanced stage of illness with remote metastases.

One of the problems in cancer treatment is the different sensitivity of different cancer types to the same therapy which additionally complicates the recovery. Therefore, we have analyzed the dependence of Isorel biotherapy on cancer type. Interestingly, in all cancer types Isorel biotherapy showed to be beneficial for the patient, with the best outcome in the group of patients with colon cancer. Many studies on mistletoe extract were done on different cancer types with an overall conclusion of benefits of mistletoe therapy[11,21,33,34]. Also, the majority of studies report the influence of mistletoe extracts in the advanced stage of the illness hence targeting the most critical group of patients[21,33,34]. Yet, our analysis showed that beneficial effects were not related to cancer type, but rather due to early cancer diagnostics and therapy applied in initial stage of the illness thereby verifying our previous finding. These findings might indicate also that due to the relatively high contents of flavonoids, the mistletoe extract Isorel might be efficient modulator of oxidative homeostasis disturbed in cancer patients thus acting indeed complementary to the conventional therapies as was suggested already, in particular if future studies would reveal interference of its biotherapeutic effects with the biomodulating effects of the oxidative stress mediators, such as 4-hydroxynonenal, as was recently observed in vitro for several synthetic antioxidants[32, 35–37].

Finally, it should be said that the mistletoe extracts are in use for cancer therapy for more than 70 years, usually as adjuvant therapy, as is also the case of Isorel. The most prominent effect of Isorel therapy was observed in dependence of the stage of the illness. Moreover, the improvement in the quality of life and the psycho–emotional status with reduction of side effects of chemo/radiotherapy made these extracts popular among cancer patients as adjuvant therapy. All these findings indicate the relevance of adjuvant therapy in cancer treatment not only as anti–tumor agents which increase the effectiveness of conventional therapy but also as factors of improvement of the quality of life.

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Dedicated to Mrs. Weiss, brave fighter and faithful friend, gentle lady who joined her husband to be remembered as pioneers of the human magic of mistletoe.

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ADJUVANTNA ONKOLOŠKA BIOTERAPIJA *VISCUM ALBUM* EKSTRAKTOM ISOREL: PRIKAZ NALAZA TEMELJENIH NA MEDICINSKIM OPAŽANJIMA

S A Ž E T A K

U okviru integrativne medicine jedan od najčešće korištenih oblika adjuvantne onkološke bioterapije se temelji na vodenim ekstraktima imele (*Viscum album*). U nizu pretkliničkih i kliničkih istraživanja opisani su pozitivni učinci terapije ekstraktima imele koji uključuju inhibiciju rasta tumora uz poticanje imunološkog sustava obrane oboljelih i poboljšanje kvalitete života. Međutim, sažimanje rezultata podataka dobivenih medicinskim opažanjima za različite oblike ovakvih tretmana u osoba oboljelih od različitih oblika tumora se rijetko opisuje. Stoga ovim radom analiziramo medicinska opažanja dobivena za bolesnike liječene ekstraktom Isorel ovisno o oblicima sveukupne onkološke terapije, stadiju bolesti i tipu zloćudnog tumora. Studija uključuje kumulativne podatke dobivene za 74 bolesnika s različitim oblicima malignoma, različitih stadija bolesti koji su uz Isorel primali različite oblike konvencionalne onkološke terapije, pretežito kombinaciju kirurškog zahvata i radioterapije. Uspješnost adjuvantne bioterapije je evaluirana prema ishodu kao 1) bez znatnijih terapijskih učinaka (15% bolesnika), 2) prevencija recidiva bolesti (47%), te nestanak bolesti (38%), pri čemu treba napomenuti da niti u jednog bolesnika nije zabilježeno pogoršanje zdravlja. Stoga dobiveni rezultati konvencionalnih onkoloških terapija u kombinaciji s adjuvantnom terapijom Isorelom ukazuju na korisnost ovakvog integrativnog medicinskog pristupa u 85% onkoloških bolesnika, bez neželjenih popratnih pojava.