

Exploring an herbal “wonder cure” for cancer: a multidisciplinary approach

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Abstract

Context and objectives The unmonitored use of herbal medicinal remedies by patients with cancer presents a significant challenge to oncology healthcare professionals. We describe an increasingly popular herbal “wonder drug,” *Ephedra foeminea* (Alanda in Arabic), whose use has spread from the Palestinian patient population throughout the Middle East. We conducted a multicentered and multidisciplinary collaborative research effort in order to understand the potential benefits and harms of this popular herbal remedy.

Methods We conducted an in-depth search of the medical literature, both traditional and modern, for any mention of the clinical use of Alanda for the treatment of cancer. We then tested the remedy, first for toxic ephedra alkaloid components and then for anticancer effects, as well as effects on the cytotoxic activity of chemotherapy agents (cisplatin and carboplatin) on breast cancer cell cultures.

Results We found no mention in the literature, both conventional and traditional, on the use of Alanda for the treatment of cancer. Laboratory testing did not find any toxic components (i.e., ephedra alkaloids) in the preparation. However, in vitro exposure to Alanda led to a reduced cytotoxic effect of chemotherapy on breast cancer cell cultures. **Conclusions** The use of an integrative ethnobotanical, laboratory and clinical research-based approach can be extremely helpful when providing nonjudgmental and evidence-based guidance to patients with cancer, especially on the use of traditional herbal medicine. The effectiveness and safety of these products need to be examined by integrative physicians who are dually trained in both complementary medicine and supportive cancer care.

Keywords Integrative medicine · Herbal medicine · Complementary medicine · Quality-of-life (QOL) · Drug–herb interactions · *Ephedra foeminea*

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Introduction

Alanda (*Ephedra foeminea* Forssk., or *Ephedra campylo-poda* C.A.Mey.) is the Arabic name for a low stalky Eurasian shrub from the Ephedraceae family, ubiquitous to northern Israel and across the southeastern Mediterranean. Unlike other Ephedra species, such as the popular Chinese medicinal herb Ma Huang (*Ephedra sinica* Stapf, or *Ephedra ma-huang* Tang S.Liu), little is known about Alanda in the treatment of cancer, and it has only been mentioned in traditional Arab medicine as a treatment for anxiety and skin rash (Philips 1958). Until recently, there has not been any evidence that patients with cancer were using this herbal remedy for treating their illness. In a regional survey of oncology healthcare professionals from 16 Middle Eastern countries, who were asked to provide a list of herbs which were popular among their patients, Alanda was not among the 44 herbal products mentioned (Ben-Arye et al. 2016a). However, as early as October 2013 many of the Arab-speaking patients, who had been referred by their oncologists to the integrative oncology program (IOP) (part of the Oncology Service of the Haifa and Western Galilee District, Clalit Health Services, Israel), reported using Alanda with the belief that the herb could “cure” their disease (Ben-Arye et al. 2012).

The introduction of a new medicinal herb, which was becoming increasingly popular among Arab-speaking patients referred to the IOP, was without precedent. Many of these patients were bringing Alanda stalks to the IP consultation, asking about the effectiveness and safety of the herb. They had heard about Alanda through an Israeli news program, which had been uploaded to YouTube. In the video, a shepherd from the village of Tura in the Palestinian Authority describes how he had been diagnosed with cancer, had undergone surgery and chemotherapy and was finally told that the tumor was no longer responding to treatment. A sheep in his flock became ill and began to chew on the stalks of an Alanda brush nearby. When the animal was miraculously “healed,” the shepherd decided that he should try this treatment himself. He gathered a bunch of Alanda vines, boiled them in tap water and drank the concoction numerous times throughout the day. According to the shepherd’s testimony in the YouTube video, within a short period of time his disease resolved completely, and his oncologist was “amazed” by the “miracle.” Many articles in the printed and online media appeared on the curative effects of Alanda, in both the Israeli and Palestinian media. Israel’s Channel One, the government-sponsored television channel, aired a segment of the nightly news which talked about Alanda, and the published media was rife with stories of patients who were “cured” or “in remission” after taking the herbal remedy (<https://www.youtube.com/watch?v=-pvk49ar8PI>; <https://www.youtube.com/watch?v=UvnkGnSKF58>).

News of Alanda began to spread to other countries in the region as well, with reports of the “wonder cure” appearing on television channels from Jordan to the United Arab Emirates (<https://www.youtube.com/watch?v=nlk9WycENVI>; https://www.youtube.com/watch?feature=player_embedded&v=_va60JRYQpc). Eventually, we received a query from an IP working at the Memorial Sloan-Kettering Cancer Center in New York. He asked about a patient of his, a Palestinian woman who had come to him for treatment of a biliary tract tumor (cholangiocarcinoma), who was using an herbal remedy called “Alanda” to treat her cancer, in addition to conventional chemotherapy. He remarked that the stalks of the herb looked very similar to the popular Chinese medicinal herb Ma Huang (*E. sinica* Stapf).

The integrative physicians at the IOP became concerned about the widespread and unmonitored use of Alanda by their patients, especially in light of the fact that little was known about the herb, from both conventional and traditional sources. They were especially concerned about the potential for toxic effects, such as those associated with Ma Huang, as well as negative interactions with chemotherapy agents. Ma Huang has been banned in most countries due to its ephedrine alkaloid-related effects, which have been linked to significant cardiovascular and central nervous system morbidity, possibly even mortality (Woolf et al. 2005). And while it has been shown that *Ephedra foeminea* does not contain any ephedra-related components (1*R*,2*S*-ephedrine or 1*S*,2*S*-pseudoephedrine) or metabolic precursors (1-phenylpropane-1,2-dione and *S*-cathinone) (Krizevski et al. 2010), the local Alanda plants and extracts had not yet been evaluated for this purpose. In order to gain a better understanding of what Alanda was and what it could do for and to our patients, we reached out to other medical centers and laboratories in Israel. The main goal of this collaborative effort was first and foremost to establish the safety of the herbal remedy, which our patients were using, and then test its effectiveness as an anticancer agent.

Materials and methods

Initial assessment and consultation process

Clinical interactions at the IOP are documented in a research-based registry protocol. The protocol was approved by the Ethics (Helsinki) Committee of the Carmel Medical Center, Haifa, Israel, and registered at ClinicalTrials.gov (NCT01860365). Procedure at the IOP requires that patients arrive at the initial integrative physician (IP) consultation with a structured referral letter from their oncologist, oncologist nurse or social worker. Patients are seen by one of the programs IPs who are conventional

physicians with extensive training in both complementary medicine and supportive cancer care. The initial assessment consists of a semi-structured interview that addresses the patient's previous and current use of complementary and traditional medicine (CTM), with specific questions on the use of herbal medicine following the cancer diagnosis. At the end of the initial IP assessment, patients are referred to the IOP's team of CTM practitioners, who provide a wide range of therapies with the goal to improve quality-of-life (QOL)-related outcomes. Treatments are chosen based on the patient's preferences, symptom severity and the level of research supporting efficacy and safety of the treatment.

During the IP consultation, patients are encouraged to ask about their use of herbal medicine (Almog et al. 2014). The IP can then recommend specific herbal and other nutritional supplements, based on a search of the scientific literature (e.g., PubMed) vis-à-vis the effectiveness and safety of the herbal products in question, while taking into consideration the potential for interactions with chemotherapy agents and other medications being used. The potential for herb–drug interactions is also examined using additional evidence-based resources, such as the Memorial Sloan-Kettering Herb Reference site (2015) and the Natural Medicines Comprehensive Database (2015).

Examining the prevalence of Alanda use

In order to understand the prevalence of Alanda use among Palestinian and Israeli patients with cancer, we first examined the Arab population in the north of the country, where this phenomenon had apparently begun. For this purpose, we initiated a parallel study, which took place at the Watani Hospital in Nablus, Palestine. The study was conducted by researchers from the Biodiversity and Environmental Research Center between August and October 2014. Questionnaires consisting of 11 questions asking patients about demographic characteristics, with an additional 18 questions on the use of and attitudes toward CTM and herbal medicine, were distributed. Patients with cancer of any stage aged 18 years and older were eligible for participation in the study, and a research assistant gave them the questionnaires during the consultation with the patient's oncologist or during treatment. Respondents were asked to respond only with respect to those CTM treatments, which they were using within the context of their cancer diagnosis or chemotherapy regimen.

Searching conventional and traditional medical resources

We conducted an extensive search of the conventional medical literature using a number of online search engines

(PubMed, TOXLINE, EMBASE and Google Scholar), as well as textbooks (i.e., medical toxicology, medical botany and herbal medicine) and the MICROMEDEX Healthcare Series databases (Poisonindex, AltMeDex and Martindale, Truven Health Analytics Inc., 2014). Our search found no clinically relevant evidence that *E. foeminea* (or Alanda) was ever examined for its effect in the treatment of cancer. We then turned to traditional sources, including the medieval Arabic and Hebrew medical and pharmacological literature (Lev and Amar 2008). Primary sources included a wide myriad of medical books, focusing on information provided in the *Materia Medica* and pharmacopeia in Arabic, Hebrew and Judeo-Arabic. We also searched secondary sources, such as edited and translated books and research papers (Lev 2002, 2006). For the purpose of this search, we used the term ephedra, as well as Arabic nomenclature with terms such as 'alanda (علنده), 'alad (علد) and qdyab (قضييب). No mention was found in the literature on the use of this herbal remedy for the treatment of cancer.

Testing for effectiveness and safety

Our next step was to examine the effect of Alanda in the form being used by patients with cancer. For this purpose, we used an extract which had been prepared by the father of a 36-year-old male patient with testicular cancer, who was undergoing treatment with bleomycin, etoposide and cisplatin (BEP protocol). The sample was sent to the Israeli Police Substance Analysis Laboratory in the Division of Identification & Forensic Sciences, in Jerusalem. There, it was examined (in duplicate) using a gas chromatography–mass spectrometry (GC–MS) assay.

A second sample of Alanda was harvested by an Israeli Druze practitioner of traditional Arab medicine, who had visited the Palestinian shepherd from Tura and learned first-hand how to prepare the concoction. This sample was prepared at the Department of Weed Science in the Newe-Yaar Research Center, where freshly picked Alanda stems (24 g) were cut into small pieces, boiled in 0.5 L of tap water for an hour and then cooled to room temperature. The broth was filtrated using a cloth sheet. The second preparation was then sent to the Galilee Technology Center in Kiryat Shmona, Israel, where the remedy was incubated with breast cancer cell lines (MDA-MB231 and SKBR3) for 72 h. An XTT assay was used to test the cytotoxic effects of the extract, using the chemotherapy agents, carboplatin and cisplatin, as controls. Alanda (*E. foeminea*) seeds are currently preserved in the “Collection and storage of seeds of crops wild relatives in Israel” at Agricultural Research Organization (ARO), Volcani Center, P.O.B 6, Bet Dagan 50250, Israel.

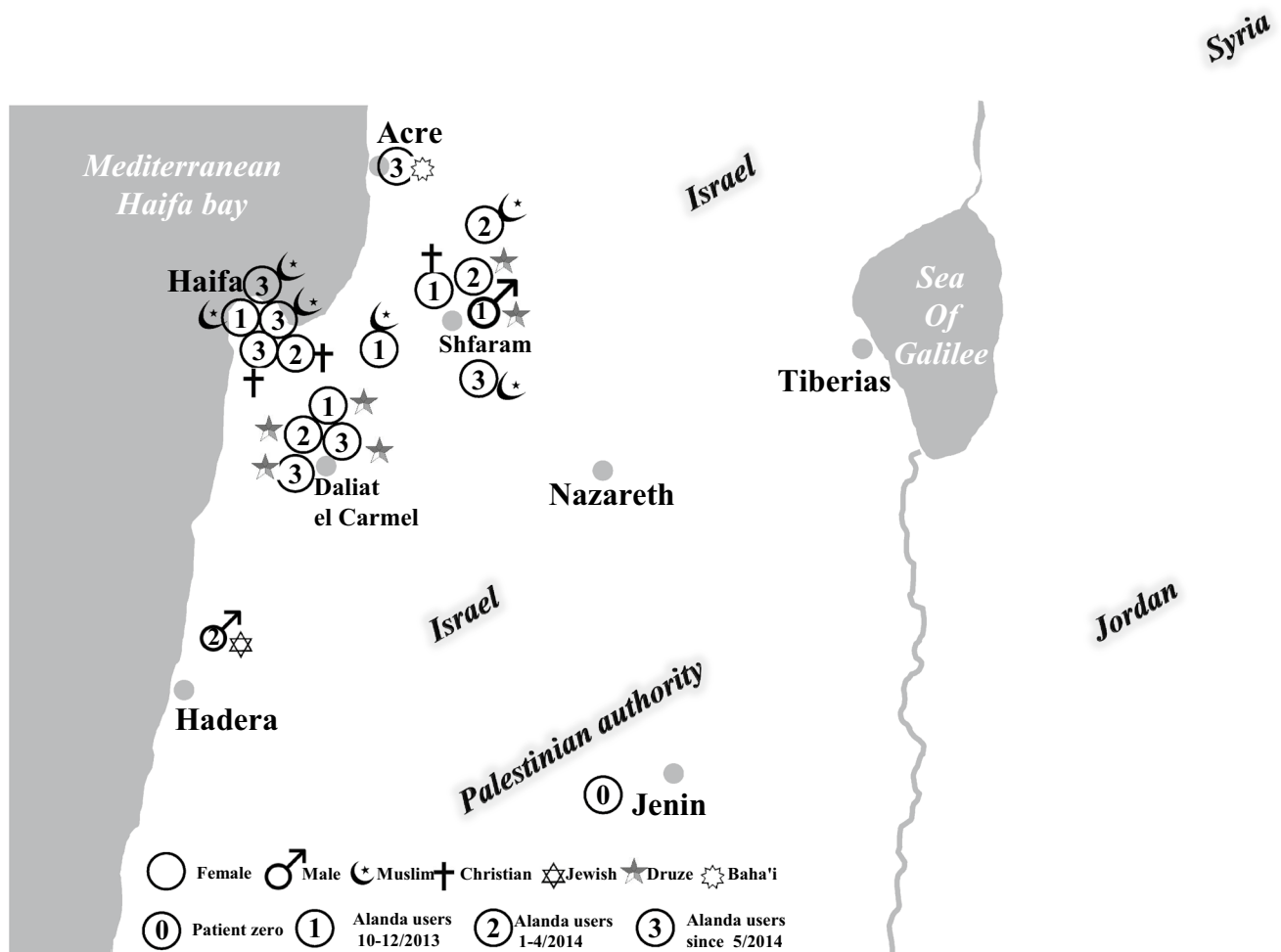


Fig. 1 Cross-cultural mapping of the spread of Alanda use among patients with cancer in northern Israel, following a YouTube video on “patient zero” (Palestinian Authority)

Results

Prevalence of Alanda use

The use of Alanda was first documented in the IOP records in October 2013. Until then, there had been no mention of this herb during the IP consultations or in the electronic patient records. It appeared that the use of Alanda was spreading, moving from the Muslim and Druze Arab communities in northern Israel to the Jewish and Bahai communities, among others (Fig. 1). The first cohort of 18 patients using Alanda was characterized by a high frequency of Arab speakers (16, 88.8 %) and of female gender (14, 77.7 %). The median age of the cohort was 52 years, with a high prevalence of Alanda use among patients with breast cancer (10, 55.5 %), half of them with advanced and metastatic disease (9, 50 %). Among this cohort, 17 of 18 patients reported using Alanda in conjunction with their chemotherapy regimen, which included agents such as

Adriamycin and cyclophosphamide (Cytoxan), platinum and taxanes-based drugs and capecitabine (Xeloda).

Most of the patients using Alanda reported that they had learned of the herb from the internet, family members or friends. They all expressed a belief that the herbal remedy would either reduce the tumor size or at the least delay disease progression. In general, the patients or their relatives had harvested the plant themselves, or else obtained it without cost and prepared the potion at home. The method of preparation varied considerably, as did the estimated dosage, which ranged from 100 to 500 mL, two to three times a day, each time using between 350 and 500 g of Alanda stems which were boiled for two hours in 2–7 L of water. In the study conducted at the Watani Hospital in Nablus, 53 of 100 patients with cancer reported using Alanda during chemotherapy. This contrasted greatly with the findings of a previous study, which took place at the same hospital between December 2010 and June 2012 (Ben-Arye et al. 2015). In the earlier study, despite a high prevalence of

herbal medicine use reported by patients, no mention was made of Alanda or related products.

During the years 2014–2015, the use of Alanda continued to spread throughout the country. More and more patients, especially Arabic speakers, were discussing the remedy with the IP at the initial and follow-up consultations, and many had either started or were considering using Alanda in addition to their conventional treatment. Alanda eventually became more prevalent among the Jewish patient population in the country, who are more likely to purchase the remedy in the form of prepared capsules or tablets. The extent of this phenomenon became even more apparent when we received an e-mail from an IP working at the Memorial Sloan-Kettering Cancer Center in New York (GD), who told us of a 79-year-old Palestinian woman with adenocarcinoma of the gallbladder who was taking an herbal remedy—Alanda—for her disease, in addition to chemotherapy.

Safety-related concerns

The GC–MS assay (Fig. 2) did not identify any ephedrine- or amphetamine-related compounds in either of the specimens. However, traces of nicotine were found, though these were believed to have come from the patient's father who had prepared the concoction and who is a heavy smoker.

Anticancer effects

The XTT assay that tested the cytotoxic activity of Alanda on breast cancer cell lines did not detect any anticancer activity of the herbal preparation (as measured by IC_{50}). However, the addition of Alanda to cancer cells in the presence of the chemotherapy agents, carboplatin and cisplatin, resulted in a dose-dependent reduction in their cytotoxic ability, by a factor of 2 and 4 in the MDA-MB231 and SKBR3 breast cancer cell lines, respectively.

Discussion

We describe a multidisciplinary and multicentered effort, whose goal was to better understand a new purported herbal “wonder cure” for cancer, Alanda (*E. foeminea* Forssk.). We found an ever-increasing use of this remedy among the varied populations of Israel and Palestine, eventually reaching other areas in the region and even globally. The story of Alanda began with “patient zero,” a shepherd who believed that the herbal remedy had “cured” him of his cancer, and spread rapidly to other patients with cancer who were looking for a “natural” remedy to treat their disease. Despite the fact that Alanda has no known tradition for healing cancer, nor any ethnobotanical basis for this

purpose, the popularity of the herb continues to increase. Our investigation showed that, unlike its related species Ma Huang (*E. sinica*), Alanda does not contain any potentially toxic ephedra alkaloids. However, we also found no benefit of this herb as an anticancer agent, at least in an in vitro setting. What we did find is that Alanda has the potential to interfere, in a dose-dependent fashion, with the cytotoxic effects of conventional chemotherapy agents.

Today's oncologists are expected to be knowledgeable in all aspects of cancer care. Yet while they may be providing state-of-the-art conventional treatment, they are often unacquainted with unconventional therapies being used by many of their patients. CTM modalities such as herbal medicine may be of benefit in certain cases, but they are not without potential risks, including adverse herb–drug interactions (Ben-Arye et al. 2016a). Integrative physicians are medical doctors with extensive training and expertise in a wide spectrum of complementary medicine modalities. IPs can serve as “gatekeepers,” mediating between conventional and non-conventional domains. The journey with Alanda began with the initial IP consultation. It then moved to an in-depth examination of the ethnobotanical and traditional medical literature and then to the laboratory, where the plant was tested for safety (the presence of ephedrine alkaloid components) and effectiveness (anticancer effects). The story of Alanda then returns now to the follow-up IP consultation, where the findings of this research are presented to our patients, enabling them and their oncology healthcare professionals to make an informed decision on the use of this product during active treatment.

Traditional herbal medicine is often perceived by patients, especially in communities with a high affinity for these practices, as a “natural” and therefore safe treatment option. At present, most countries do not have legislation, which prevents the use of Alanda or other herbal products from being prepared in backyards and other unsupervised venues. In the USA, the Dietary Supplement Health and Education Act (DSHEA) of 1994 was enacted in order to prevent claims regarding dietary supplements, which are purported “to treat, diagnose, prevent, or cure diseases” (<http://www.fda.gov/Food/DietarySupplements/ProductsIngredients/default.htm>). Yet claims of alleged herbal cancer “cures” are widespread in the written and online literature (Bonakdar 2002). In a study by Metz (2003) among patients presenting to a number of radiation oncology centers, 12 % reported purchasing unconventional medical therapies through cancer-related internet sites.

A large body of research is currently being conducted in the field of health-related informatics, in order to identify unproven cancer treatments being promoted on the internet (Yin et al. 2013). Examples of the importance of online research include the popular use of the potentially harmful amygdalin (Laetrile, containing cyanide) by patients in

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 Instrument : GCMS 5975
 Sample Name: 1909/14-1 DS DCM+DCM/NH4OH
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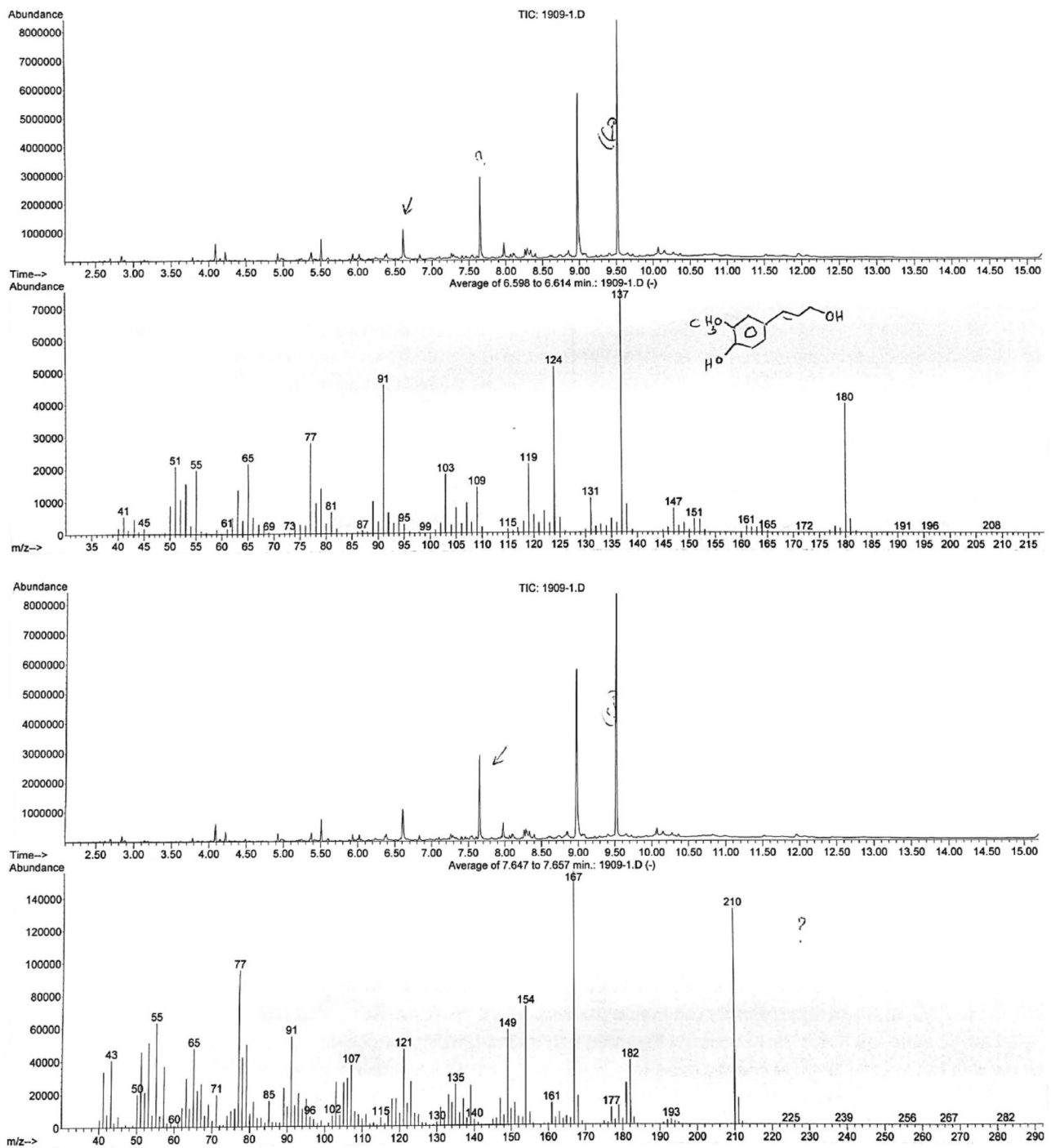


Fig. 2 *Ephedra foeminea*—GC—MS

countries such as Germany, where it is purported as a “cancer cure” (Blaheta et al. 2016), or other unproven remedies such as Essiac in the USA and Canada (Cassileth and Yarett 2012). The challenges facing today’s oncology healthcare professionals with the widespread use of dietary supplements by patients are further exacerbated when alternative medicine practitioners promote non-evidence-based herbal products. In Germany, Koehl et al. surveyed non-medical practitioners of complementary and alternative medicine who were treating oncology patients. They found that none of the treatments prescribed were being discussed with the patient’s physician on a regular basis (Koehl et al. 2014).

The unmonitored use of herbs by patients with cancer is more likely to occur in those settings where patients are seeking potent herbal remedies, and where no professional consultant familiar with this practice is available within the oncology ward in order to provide an evidence-based consultation. In the case of Alanda, the popularity of this herb was not supported by any scientific research, nor teachings of traditional Arab medicine. Rather, the herb’s popularity sailed on a populist wave, which began with a YouTube video that “went viral.” The popularity of “wonder cures” is not a new phenomenon and reflects the hope of patients with severe disease (such as cancer) for a solution, which is not being provided by modern conventional medicine. The story of Alanda may be relevant to other regions of the globe, including Western countries where cultural minorities have a high affinity for traditional herbal medicine.

Another aspect of the story of Alanda that needs to be considered in regions such as Israel, Palestine and other Middle Eastern countries is that traditional medicine is closely related to patients’ health belief models. Herbal medicines are invariably an integral part of the sociomedical and cross-cultural landscape, especially among the Arabic-speaking population (Ali-Shtayeh et al. 2011; Ben-Arye et al. 2014a). In these societies, social norms often shift between concepts of the individual and identification with the collective. It is here that the accepted Western concept of patient autonomy needs to consider the values of the group as well, such as how the patient’s society views the use of traditional herbal medicine as part of the communal health belief model (Ben-Arye et al. 2016b).

IPs are frequently required to address the ethical requirement to respect their patients’ health beliefs. They must design a patient-centered treatment which resonates with the patient’s biopsychosocial-spiritual elements of care, while at the same time providing evidence-based medical guidance on safety and effectiveness. The information provided during the IP consultation is important for both patients and the oncology healthcare professionals responsible for their care. It is in the setting of the IP consultation at the IOP, where the use of Alanda during active chemotherapy was raised, stimulating a multidisciplinary,

multicentered and multicultural collaborative effort by an international team of researchers and clinicians. This effort will hopefully serve as a model for testing other new “wonder cures,” helping IPs provide the information necessary for their patients and oncology healthcare practitioners to make an informed decision on treatment options.

The approach we used in our investigation of Alanda is presented in Fig. 3. It is first important to establish a realistic framework in which the most effective and efficient outcomes of the consultation can be achieved. In most cases, even the most in-depth investigation by an IP, with the cooperation of a multidisciplinary team of researchers and clinicians, will lead to conclusions on the effectiveness and safety of the herbal product in question which are limited, at best. While some herbal products have clear evidence regarding safety-related concerns (e.g., Ma Huang), in most cases the information available is limited to in vitro or in vivo animal studies. Still, preliminary recommendations are undoubtedly better than no recommendations at all, or even to the prohibition of any and all use of herbal medicinals by patients. The latter approach ignores patients’ expectations and health belief models and will most likely result in subsequent continuation of this practice in an undisclosed and thus unmonitored fashion.

The construction of an effective and safe treatment plan for the use of complementary medicine therapies, including herbal medicine, requires that five steps be taken by the IP, the patient and the oncology healthcare professional (Fig. 3). It is imperative that the use of herbal medicine and an accurate list of the herbal products being used (on being considered for use) be identified. This requires an awareness and understanding of the terms and concepts, whether scientific (e.g., *E. foeminea* Forssk.) or cultural (Alanda). An accurate botanical classification of the products in question should follow, with quantification of the active components through accepted scientific methods (e.g., high-performance liquid chromatography, HPLC) and assurance of quality (e.g., good manufacturing practice, GMP), in order to rule out any contamination by toxic substances or conventional medications (Ben-Arye et al. 2014b).

The next steps toward a better understanding of the implications of herbal medicine use need to take place during the meeting with the IP. It is during this interaction that the patient’s expectations and health belief model can be discussed, and the effectiveness and safety of the relevant herbal remedy examined. For this purpose, the IP should seek out the help of a multidisciplinary team, which is comprised of a medical historian, who can provide information on the herbal product within a traditional medicine perspective; a licensed clinical herbalist, who can provide guidance on modern traditional medicine practice; a research assistant, who can perform in-depth research of the literature; a basic science researcher, who can examine the in vitro

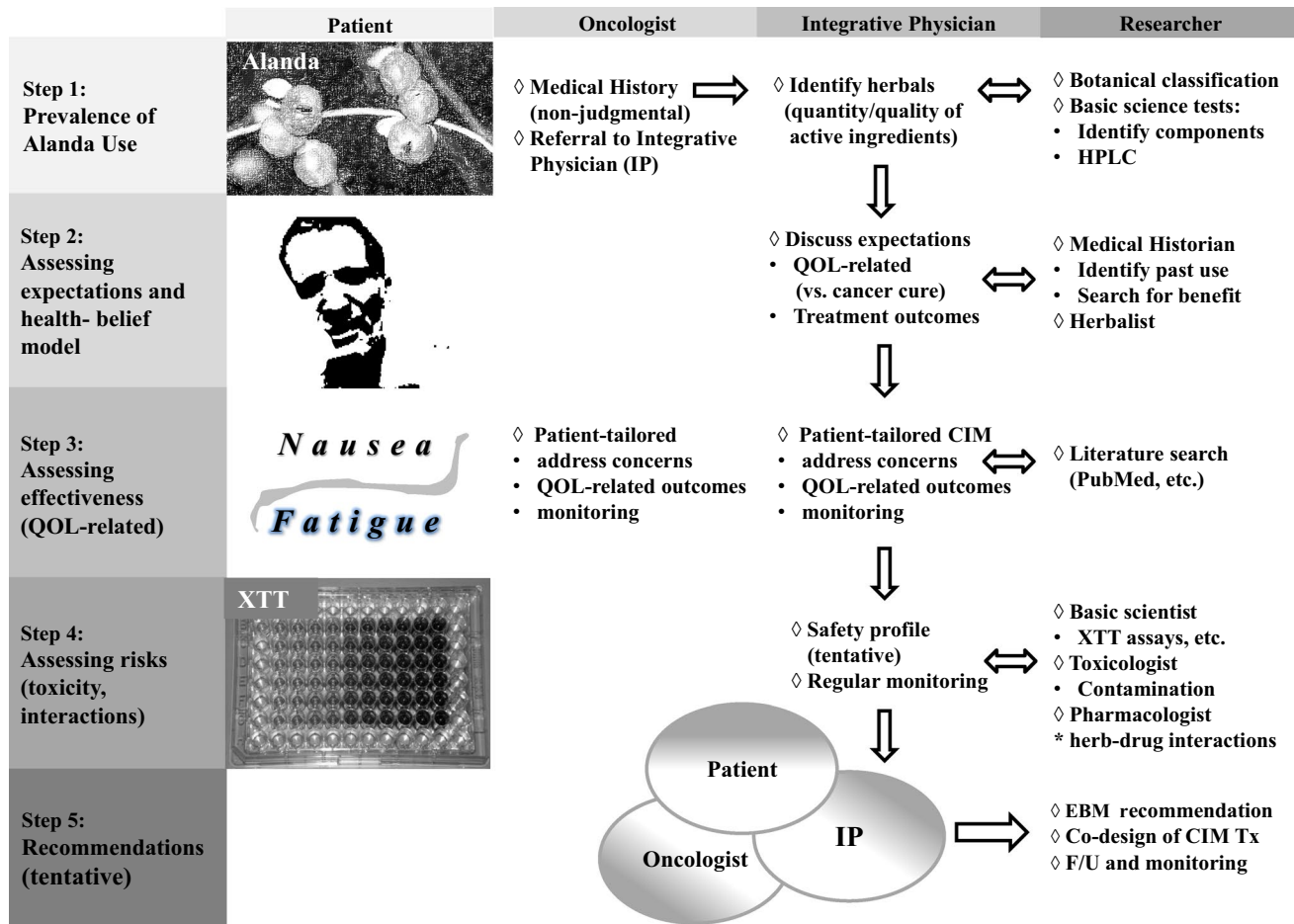


Fig. 3 Approach to establishing evidence-based guidance for the use of Alanda* during chemotherapy

effects of the herb on cancer cells, in a “real-time” setting, following the IP consultation; and others from fields such as toxicology and pharmacology.

During the consultation, the IP can also explore patient-centered aspects of herbal medicine use (e.g., what they hope to achieve from the use of the herbs; how this practice connects with their health belief; what are the most significant QOL-related concerns), as well as more general aspects regarding the potential implications for the patient and others in their community. It is also important to understand how the patient heard of the herbal remedies in question (e.g., printed and online media; complementary or traditional medicine practitioner; family members or friends) and to become familiar with the products being marketed through this venue.

The final stages of the process again involve the IP, the patient and the oncology healthcare professional responsible for the patient’s care. It is at this point that the potential risks of herbal medicine use should be addressed. At this phase, the findings of an in-depth examination of all relevant information from the medical literature can be

presented, as can the findings of research testing of the herbal products in question for toxic or other harmful components. Finally, the impact of the herbal product on the anticancer activity of anticancer agents can be discussed. This last step should be done through a search of the scientific literature and, if possible, “real-time” in vitro testing of cytotoxic effects of treatment, using accepted scientific methods (e.g., XXT assays). Although the findings of these studies may be limited to the in vitro setting, which do not necessarily reflect the true clinical implications of the combined therapy, they can provide the IP with a point of reference for future research while providing important information to use when advising the patient. At the end of these processes, an open and nonjudgmental discussion needs to take place between the IP, the patient and the oncology healthcare professional. The conversation needs to address the limitations of any recommendations, which are to be made, and presents an opportunity to suggest other integrative treatments which may be of benefit in reducing the symptom load and improving QOL-related outcomes.

In conclusion, there are many popular herbal “wonder cures,” which are being used by patients with cancer, some of which can potentially cause harm, either through directly toxic effects or interactions with oncology drugs. Our study suggests that the way to detect and monitor the uncontrolled use of these products is through the establishment of an integrative oncology consultation. This should be provided to all patients undergoing chemotherapy and palliative care and should take place within the conventional oncology setting. The multidisciplinary and multicentered collaboration, which has been presented here, should serve as a model for the investigation of other herbal products. This is especially important for those healthcare professionals working in countries where there is a high affinity among patients to herbal remedies, such as in the Middle East. This joint effort can help patients receive evidence-based guidance, ensuring the effective and safe use of herbal medicine. Products whose goal is to improve quality of life and well-being need to be tested as well, integrating the “bedside” with the “bench” in a bidirectional ethnopharmacological effort. The integration of CTM within the conventional oncology setting, in which IPs provide guidance on this subject, may serve as a key to such an approach.

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Authors' contribution All authors contributed equally to the design and drafting of the article.

Compliance with ethical standards

Conflict of interest Prof. Eran Ben-Arye declares that he has no conflict of interest. Dr. Jamal Mahajna declares that he has no conflict of interest. Dr. Radi Aly declares that he has no conflict of interest. Dr. Mohammed Saleem Ali-Shtayeh declares that he has no conflict of interest. Prof. Yedidia Bentur declares that he has no conflict of interest. Prof. Efraim Lev declares that he has no conflict of interest. Dr. Gary Deng declares that he has no conflict of interest. Dr. Noah Samuels declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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