Original Article

Potential Risks Associated With Traditional Herbal Medicine Use in Cancer Care: A Study of Middle Eastern Oncology Health Care Professionals

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BACKGROUND: The authors assessed the use of herbal medicine by Middle Eastern patients with cancer, as reported by their oncology health care professionals (HCPs). Herbal products identified by the study HCPs were evaluated for potential negative effects. **METHODS:** Oncology HCPs from 16 Middle Eastern countries received a 17-item questionnaire asking them to list 5 herbal products in use by their patients with cancer. A literature search (PubMed, Micromedex, AltMedDex, and the Natural Medicine Comprehensive Database) was conducted to identify safety-related concerns associated with the products listed. **RESULTS:** A total of 339 HCPs completed the study questionnaire (response rate of 80.3%), identifying 44 herbal and 3 nonherbal nutritional supplements. Safety-related concerns were associated with 29 products, including herb-drug interactions with altered pharmacodynamics (15 herbs), direct toxic effects (18 herbs), and increased in vitro response of cancer cells to chemotherapy (7 herbs). **CONCLUSIONS:** Herbal medicine use, which is prevalent in Middle Eastern countries, has several potentially negative effects that include direct toxic effects, negative interactions with anticancer drugs, and increased chemosensitivity of cancer cells, requiring a reduction in dosedensity. Oncology HCPs working in countries in which herbal medicine use is prevalent need to better understand the implications of this practice. The presence of integrative physicians with training in complementary and traditional medicine can help patients and their HCPs reach an informed decision regarding the safety and effective use of these products. ***Cancer*** **2016;122:598-610.** *© 2015 American Cancer Society.*

KEYWORDS: complementary traditional medicine, drug-herb interaction, integrative medicine, physician-patient communication, quality of life.

INTRODUCTION

The use of herbal medicine by patients with cancer may result in potentially negative effects that can impact the efficacy and safety of conventional anticancer treatments. Greater than 35% of patients with cancer in the United States report using herbal medicine during chemotherapy, with this rate exceeding 50% in developing countries.[1,2] Between 20% and 70% of patients using complementary and traditional medicine (CTM), including herbal agents, are often reluctant to disclose this practice to their conventional medical professional.[3] This results from an anticipated negative response (either disapproval or a general lack of interest).[3]

In light of the increased use of CTM by patients with cancer, many of the leading cancer centers have begun to provide patients with an evidence-based consultation and subsequent CTM treatments, including herbal medicine. However,

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to the best of our knowledge, only a few of these centers offer this service as part of standard care in their conventional oncology setting.[4] At the same time, many oncology health care professionals (HCPs) report that they do not believe they are adequately informed about herbal medicine, and lack competence in this field in their daily practice.[5] As a result, many patients are seeking advice from family members, friends, or nonconventional medical practitioners.[6,7]Nevertheless, many patients expect conventional HCPs to provide up-to-date information and guidance on CTM treatments, including herbal medicine, as part of the medical consultation.[8] Greater than 85% of patients have reportedly admitted they would discontinue the use of herbal agents if a potentially harmful herb-drug interaction was suspected.[9]

Much has been published regarding the potential for interactions between herbal products and conventional drugs, especially in the field of oncology. The research has focused primarily on the effects of herbal components on the induction[10] and bioavailability of chemotherapy agents,[11] and is almost exclusively preclinical, in which cancer cell lines and animal models are exposed to combinations of herbal products and chemotherapeutic agents.[12,13] The potential for herb-drug interactions is attributed primarily to the drug-metabolizing enzyme cytochrome P450 (CYP450) system, of which CYP3A4 is the most predominant.[14] Other factors such as the transporter P-glycoprotein have been examined as well.[15] The findings of this research are often contradictory, demonstrating either antagonistic effects,[16] additive effects,[17] synergy,[18] or no interaction whatsoever.[19] Clinical research has revealed several directly toxic effects of herbal products,[20,21] as well as alterations in the pharmacokinetics of anticancer drugs,[22] although these findings are often contradictory as well.[23]

The conflicting findings with regard to herb-drug interactions have precluded the development of accepted guidelines. As a result, there are those in the medical profession who have issued an across-the-board recommendation to avoid the use of all herbal products during active anticancer treatment.[24] Although this may be prudent, it is a somewhat unrealistic solution for oncology HCPs working in communities in which herbal medicine is an integral part of societal norms. Abstention from herbal medicine may not be acceptable to patients, their family members, or their community. This approach also may impede physician-patient communication[25] and may be regarded as unethical and disrespectful to patient autonomy.[26]

The Middle East is a region with a high affinity for CTM, including the use of herbal medicines, which has been reported for >60% of patients receiving adjuvant or palliative care.[27] We found that Middle Eastern oncology HCPs have a generally positive attitude toward the integration of CTM in supportive cancer care.[28] In the current study, we collated and analyzed additional data from this cohort, examining specific herbs listed by HCPs as being used by their patients undergoing active oncology treatments. We then searched the medical literature for potentially harmful outcomes associated with these products, such as directly toxic effects and herb-drug interactions. This enabled us to develop a pragmatic approach to the physician-patient interaction, addressing the risks of herbal medicine use in the cancer care setting.

MATERIALS AND METHODS

Background Review of the Literature

An in-depth review focusing on CTM and herbal medicine use in cancer care among Middle Eastern patients was performed.[29,30] The implications on physician-patient communication were examined as well.[31,32]Preclinical and clinical research findings (English language) were searched using 4 databases (PubMed, Micromedex, AltMedDex, and The Comprehensive Natural Database) published between January 2010 and March 2015.[33] A Medical Subject Headings (MeSH)search using the scientific and commonly used names of the identified herbal products was conducted, as was a search using the following terms: "herb-drug interaction," "adverse effects," "sideeffects," "safety," "risk," "toxic/toxicity," "bioavailability," "induction," "absorption," "inhibition," "synergism," and "chemosensitization." Boolean operator words ("AND," "OR"), as well as asterisks (*) were used in conjunction with the keywords of the search to ensure that all of the variations of the terms were included.

Study Questionnaire

The study HCPs were asked a series of questions regarding demographic and professional characteristics, and were then asked to list the 5 leading herbs being used by their patients. The term "complementary traditional medicine" (CTM) was used to describe those therapies that are considered to be alternative, natural, folk/traditional, complementary, or integrative medicine. The study questionnaire was based on a validated questionnaire that was developed by us in a previous study that explored the perspectives of patients in Israel and Palestine regarding the integration of CTM within supportive cancer care.[34,35] The study questionnaire was reviewed by a focus group of 12 HCPs from a variety of age and sex groups, religious self-definitions, and cultural backgrounds, as well as other HCPs working in an oncology setting and with training

TABLE 1. Demographic Characteristics of Oncology HCPs[a]

Characteristic	Total Cohort N=339 No. (%)	HCPs Listing Herbal Products N=201 No. (%)	HCPs Not Listing Herbal Medicine Use N=138 No. (%)	*P*
Mean age ± SD (median), y	41.35 ± 9.37 (40)	40.63 ± 8.52 (40.5)	42.39 ± 10.44 (40)	.1
Sex				
Male	157 (48.0)	81 (41.5)	76 (57.6)	
Female	170 (52.0)	114 (58.5)	56 (42.4)	.005
Religion				
Muslim	203 (63.2)	137 (71.4)	56 (51.2)	.0004
Christian	51 (15.9)	24 (12.5)	27 (20.9)	.061
Druze	3 (0.9)	2 (1.0)	1 (0.8)	1.00
Jewish	64 (19.9)	29 (15.1)	35 (27.1)	.01
Profession				
Physician	198 (58.4)	114 (56.7)	84 (60.9)	.5
Researcher	55 (16.2)	38 (18.9)	17 (12.3)	.13
Paramedical practitioner	64 (18.9)	41 (20.4)	23 (16.7)	.4
Complementary medicine training	5 (1.5)	4 (2.0)	1 (0.7)	.65
Medical director	14 (4.1)	13 (6.5)	1 (0.7)	.01

Abbreviations: HCP, health care practitioner; SD, standard deviation.
[a] Oncology HCP refers to oncologists, oncology surgeons, family physicians, oncology nurses, psychooncologists, and oncology paramedical practitioners.

in CTM. The English version of the questionnaire was again reviewed by 16 researchers from 11 Middle-Eastern countries, all of whom were members of the Middle East Cancer Consortium (MECC).[36] The final version contained 17 questions, with an open-ended question asking respondents to list the 5 leading herbal compounds being used by their patients during cancer treatment (see online Supporting Information).

Distribution of Study Tool

The final version of the study questionnaire was mailed to a list of HCPs that included oncologists, oncology surgeons, family physicians, oncology nurses, psychooncologists, and oncology paramedical practitioners. All participants were Middle-Eastern practitioners treating patients with cancer on a regular basis who had attended MECC workshop programs in supportive and palliative care. Additional HCPs who participated in the workshops were contacted using a snowball, nonprobability sampling methodology. Initially, a smaller group was recruited, on the condition that they were acquainted with at least 20 additional HCPs who met the study inclusion criteria.

Study Sites and Participants

The study was conducted between June 2012 and July 2013, during which time the questionnaire was sent to HCPs from the following 16 Middle Eastern countries: Cyprus, Egypt, Iraq, Israel, Jordan, Lebanon, Oman, Pakistan, Palestinian Authority, Qatar, Sudan, Syria, Tunisia, Turkey, United Arab Emirates, and Yemen. Participating HCPs were affiliated with 63 cancer care and/or academic centers in the region.

RESULTS

Of the 422 HCPs contacted from 16 Middle Eastern countries, 339 returned the study questionnaire (response rate of 80.3%). Of these, 201 respondents (57.5%) from 15 countries listed at least 1 herbal medicinal product as being used by their patients. The demographic characteristics of HCPs reporting herbal medicine use were similar to those whose patients did not use herbal medicines (Table 1). Herbal medicine use was reported more frequently among female HCPs ($P = .005$) and among Muslim respondents compared with their non-Muslim counterparts ($P = .0004$).

Rates of herbal medicine use and the products identified are shown in Table 2. Countries with high rates of herbal medicine use included Turkey (as reported by 89.7% of respondents), the Palestinian Authority (78.1%), Lebanon (69.2%), Qatar (72.7%), and the United Arab Emirates (62.5%). In total, 47 products were identified, 44 of them by the scientific nomenclature provided. The remaining 3 products were nutritional supplements (honey, camel's milk, and Zamzam water from Mecca in SaudiArabia). The most frequently identified herbal products included *Urtica dioica* and *urens* (stinging nettle; Turkey), *Curcuma longa L.* (turmeric; 5 countries), *Allium sativum L.* (garlic; 6 countries), *Nigella sativa L.*

TABLE 2. Oncology HCPs Reporting on Specific Herbs Used by Their Patients With Cancer From 16 Middle Eastern Countries

Country	No.	Percent Reporting Use of Herbal Products (% of HCPs)	No. of Herbal Products Reported	Most Commonly Reported Products
Total cohort	339	201 (59.3)	44	
Cyprus	30	11 (36.7)	8	Allium sativum L. (garlic)
Egypt	12	7 (58.3)	5	Honey
Iraq	11	0 (0)	0	
Israel	76	29 (38.2)	14	Curcuma longa (turmeric)
Jordan	46	18 (39.1)	11	Nigella sativa L.(black cumin)
Lebanon	26	18 (69.2)	11	Allium sativum L. (garlic)
Oman	1	1 (100)	1	
Palestinian Authority	32	25 (78.1)	11	Arum palaestinum Boiss.
Pakistan	1	1 (100)	1	
Qatar	11	8 (72.7)	6	Camel milk
Sudan	2	1 (50)	1	
Syria	1	1 (100)	1	
Tunisia	3	1 (33.3)	1	
Turkey	68	61 (89.7)	14	Urtica dioica/urens(stinging nettle)
United Arab Emirates	16	10 (62.5)	6	Daucus carota sativus (carrot)
Yemen	3	3 (100)	3	

Abbreviation: HCPs, health care practitioners.

(black cumin; 6 countries), *Zingiber officinale* (ginger; 5 countries), camel's milk (3 countries), *Camellia sinensis L.* (green tea; 4 countries), and *Arum palaestinum Boiss.*(4 countries).

Safety-Related Concerns

A total of 29 of the 44 herbal products identified were associated with safety-related concerns (65.9%) (Table 3).[37-93] These were grouped according to 3 predominant themes: 1) potentially harmful herb-drug interactions with a reduction in bioavailability (and thus efficacy) of anticancer agents, or increased drug levels with increased toxicity (15 herbs; 34.1%); 2) directly toxic effects of herbal compounds and metabolites (18 herbs; 40.9%); and 3) enhanced anticancer effects of conventional treatment through either synergy with herbal components or chemosensitization of cancer cells, thereby increasing the response to treatment (7 herbs; 15.9%).

Herb-Drug Interactions

Several potentially negative herb-drug interactions were identified. These were mediated primarily through the cytochrome P450 enzymes, primarily induction of CYP3A4.[37,38] CYP induction can cause a reduction in bioavailability and subsequently the effectiveness of anticancer agents,[39-41] whereas enzyme inhibition can increase the risk of toxicity, such as that observed with etoposide, paclitaxel, vinblastine, and vincristine.[42-47] Additional effects on factors such as intestinal P-glycoprotein, which inhibits drug absorption, can alter the bioavailability of anticancer drugs such as etoposide.[48-50] The inhibition of boronic acid–based proteasome inhibitors (eg, bortezomib)[51] or the transport of irinotecan and its metabolite, SN-38, can increase biliary removal with an increase in the half-life of the drug[52]; a reduction in organic anion transporting polypeptides can increase the absorption of chemotherapy agents such as etoposide, irinotecan, methotrexate, and paclitaxel[53]; gingko biloba can inhibit paclitaxel metabolism (in vitro)[54]; and an increase in the bioavailability or a decrease in the activity of tamoxifen in estrogen-responsive tumors may occur,[55-58] as well as a reduction in the drug's active metabolite levels via CYP2D6 inhibition.[59,60]

Direct Herb-Related Toxicity

Many of the herbal products identified were found to have directly toxic effects, such as an increased risk of bleeding with anticoagulant and antiplatelet treatment by *Allium sativum* (garlic),[61] *Camellia sinensis L.*,[62] *Cuminum cyminum L.*,[63] *Curcuma longa L.* (turmeric),[61] *Foeniculum vulgare*,[64] *Ginkgo biloba L*,[65,66] *Hippophae rhamnoides L*,[67] *Linum usitatissimum L.*,[68] *Nigella sativa* L.,[69] *Olea europaea*,[70] *Panax* ginseng,[71,72] *Thymus vulgaris*,[73] *Trifolium pratense L.*,[77] and *Trigonella foenum-graecum*.[75] Impaired platelet aggregation was also reported with the herbs *Vitis vinifera*[76] and *Zingiber officinale* (ginger).[77] In immune-suppressed patients undergoing bone marrow transplantation, the herbs *Ferula Asafoetida*[78] and *Zingiber officinale* (ginger) were found to have significant

TABLE 3. Safety-Related Concerns for Herbal Products Being Used by Patients With Cancer

Scientific Name of Herb (Common Name)	No. of HCPs Reporting on the Herb's Use, of Total Cohort (No. From Each Country)[a]	Herb-Drug Interactions Relevant in Cancer Treatment	Additional Safety Issues	Potential Herb-Related Augmenting Effect of Chemotherapy
Allium sativum L. (garlic)	14 (C-3, I-1, L-7, Q-1, T-1, Y-1)	Conflicting evidence about ability to induce CYP3A4 and possibly reduce activity of etoposide, paclitaxel, vinblastine, and vincristine[37]	Antiplatelet activity possibly leading to excess bleeding in patients with bone marrow suppression[61]	Not found
Aloevera L.	3 (C-1, J-1, Q-1)	None found	None found	Not found
Arum palaestinum Boiss.	5 (I-1, P-4)	None found	None found	Not found
Camellia sinensis L. (Green tea)	7 (C-1, L-2, P-3, U-1)	EGCG and other green tea polyphenols may inhibit therapeutic effect of bortezomib and other boronic acid-based proteasome inhibitors[51]; inhibit transport of irinotecan and its metabolite SN-38 in biliary elimination, resulting in half-life prolongationand possibleincrease in toxicity[52]; reduce the OATP drugs/substratesabsorption (etoposide,irinotecan, etc)[53]; and increase tamoxifen bioavalability[55]	Antiplatelet activity possibly leading to excess bleeding in patients with bone marrow suppression[62]	Not found
Capsicum species (chile peppers)	1 (L-1)	None found	None found	Not found
Ceratonia siliqua L. (carob)	2 (I-1, T-1)	None found	None found	Not found
Cichoriuminty bus/pumilum (chicory)	1 (P-1)	None found	None found	Not found
Cuminum cyminum L. (cumin)	1 (L-1)	None found	Antiplatelet activity possibly leading to excess bleeding in patients with bone marrow suppression[63]	Not found
Curcuma longa L. (turmeric)	18 (I-11, L-1, P-4, Q-1, T-1)	Conflicting evidence about CYP3A4 suppression that possibly increases toxicity of etoposide, paclitaxel, vinblastine and vincristine[40,42]; inhibits P-glycoprotein activity and possibly causes increased blood levels and toxicity of etoposide[48]; antagonist to etoposide preventing cell death[92]	Antiplatelet activity possibly leading to excess bleeding in patients with bone marrow suppression[63]	Curcumin reverses cisplatin resistance in cisplatin-resistant lung cancer cells by inhibiting FA/BRCA pathway[83]
Cynara scolymus (artichoke)	1 (E-1)	None found	None found	None found
Daucus carota sativus (carrot)	2 (U-3)	None found	None found	None found
Ferula asafoetida	1 (Y-1)	None found	Possible anticoagulant activity that may cause excess bleeding in patients with bone marrow suppression[78]	None found

TABLE 3. *Continued*

Scientific Name of Herb (Common Name)	No. of HCPs Reporting on the Herb's Use, of Total Cohort (No. From Each Country)[a]	Herb-Drug Interactions Relevant in Cancer Treatment	Additional Safety Issues	Potential Herb-Related Augmenting Effect of Chemotherapy
Foeniculum vulgare (fennel)	1 (E-1)	Inhibits 3A4 activity; may increases toxicity of etoposide, paclitaxel, vinblastine, and vincristine[39]; possesses estrogenic activity; might decreases tamoxifen activity in estrogen responsive tumors[56]	Antiplatelet activity possibly leading to excess bleeding in patients with bone marrow suppression[64]	None found
Ganoderma lucidum (reishi)	2 (T-2)	None found	None found	Synergistic interaction between and Ganoderma triterpenes and doxorubicin in HeLa cells[84];may reverse multidrug resistance in doxorubicin-resistant leukemic cell line[85]
Ginkgo biloba L.	1 (E-1)	Mild inhibition of multiple cytochrome P450 enzymes although probably not clinically relevant[41]; inhibits paclitaxel metabolism, possibly cause excess toxicity[54]	Antiplatelet effect with conflicting possible bleeding tendency[41,47]	None found
Hippophaerhamnoides L. (sea-buckthorn)	1 (J-1)	None found	Reduces antiplatelet activity possibly leading to excess bleeding in patients with bone marrow suppression[67]	None found
Hypericum perforatum L. (St. John's wort)	2 (I-1, L-1)	Induces cytochrome P450, especially CYP 3A4, which can cause reduced serum levels of chemotherapy agents with reduced efficacy of etoposide, paclitaxel, vinblastine, vincristine, cyclophosphamide, and imatinib[38]; induces P-glycoprotein activity causing reduced levels of chemotherapy such as etoposide[50]		None found
Juglans regia (walnut)	1 (U-1)	None found	None found	None found
Linum usitatissimum L. (common flax, linseed)	1 (T-1)	None found	Reduces platelet activity possibly leading to excess bleeding in patients with bone marrow suppression[68]	May enhance trastuzumab tumor-reducing effects[86]
Lipia citrodora	1 (I-1)	None found	None found	None found
Malva sylvestria (common mallow)	1 (T-1)	None found	None found	None found

TABLE 3. *Continued*

Scientific Name of Herb (Common Name)	No. of HCPs Reporting on the Herb's Use, of Total Cohort (No. From Each Country)[a]	Herb-Drug Interactions Relevant in Cancer Treatment	Additional Safety Issues	Potential Herb-Related Augmenting Effect of Chemotherapy
Matricaria chamomilla L. (chamomile)	4 (C-1, J-2, L-1)	Inhibits multiple CYP450 isoenzymes (3A4, 2D6, and 2C9) and may increase toxicity of etoposide, paclitaxel, vinblastine, vincristine, and cyclophosphamide[43]; interacts with tamoxifen via 2 possible pathways: reduced levels of active metabolite due to CYP2D6 inhibition, and antiestrogenic activity	None found	None found
Melissa officinalis (lemon balm)	3 (T-3)	May inhibit tamoxifen bio-activation and reduce activity[57]	None found	None found
Mentha L. species (mint)	2 (C-2)	Inhibits multiple cytochrome P450 isoenzymes (1A2, 2C9, 2C19, and 3A4), possibly increasing toxicity of etoposide, paclitaxel, vinblastine, vincristine, and cyclophosphamide[44]	None found	None found
Nerium oleander (oleander)	4 (T-4)	None found	Probable hepatotoxicity in a patient with metastatic sarcoma of the knee[79]	None found
Nigella sativa L. (black cumin)	12 (E-1, J-3, P-4, T-1,U-2, Y-1)	None found	Reduces platelet activity possibly leading to excess bleeding in patients with bone marrow suppression[69]	Antitumor activity of gemcitabine and oxaliplatin augmented by thymoquinone in pancreatic cancer[87]
Olea europaea (olive oil)	4 (J-2, U-2)	None found	Reduces platelet activity, possibly leading to excess bleeding in patients with bone marrow suppression[70]	None found
Panax ginseng (ginseng)	2 (I-1, L-1)	P-glycoprotein inhibition could cause elevated etoposide levels[49]; conflicting evidence regarding the effect of ginseng on CYP3A4 (induction or inhibition)[45]	Hepatotoxicity after imatinib and ginseng use in a patient with chronic myelogenous leukemia[80]; inhibits platelet activation; possibly leading to excess bleeding[71]; research in humans, however, suggests that ginseng does not affect platelet aggregation[72]	Rh2 ginsenoside hypersensitizes multidrug-resistant breast cancer cells to paclitaxel[88]
Peganum harmala	1 (P-1)	None found	None found	None found
Polygonum L.	1 (I-1)	Possesses estrogenic effect and theoretically might reduce tamoxifen efficacy[58]; conflicting evidenceregarding effects on cytochrome P450 isoenzymes (inhibition or induction)[46]	None found	None found

TABLE 3. *Continued*

Scientific Name of Herb (Common Name)	No. of HCPs Reporting on the Herb's Use, of Total Cohort (No. From Each Country)[a]	Herb-Drug Interactions Relevant in Cancer Treatment	Additional Safety Issues	Potential Herb-Related Augmenting Effect of Chemotherapy
Salvia fruticosa Mill. (sage)	4 (I-1, J-1, P-2)	None found	None found	None found
Senna alexandrina Mill.	1 (C-1)	None found	None found	None found
Solanum muricatum	1 (T-1)	None found	None found	None found
Silybum marianum L. (milk thistle)	1 (P-1)	Elevates tamoxifen levels in rat models, due to inhibition of presystemic metabolism and excess gastrointestinal absorption (inhibits CYP3A4, 2C9 and P glycoprotein)[93]	None found	Enhances breast carcinoma cell line (MCF-7) apoptosis with doxorubicin[89];In smallcell lung carcinoma cells, silibinin reverses drug resistance and acts synergistically with etoposide and doxorubicin[90]
Thymus vulgaris (thyme)	1 (J-1)	Invitro has estrogen receptor activity; may theoretically exacerbate hormone-sensitivecancers[93]	Reduces platelet activity in animals possibly leading to excess bleeding in patients with bone marrow suppression[73]	None found
Trifolium pratense L. (red clover)	1 (J-1)	Inhibits multiple cytochrome P450 isoenzymes (1A2, 2C9, 2C19, and 3A4); may increases toxicity of etoposide, paclitaxel, vinblastine, vincristine, and cyclophosphamide[47]; possibly inhibits tamoxifen effects due to potential estrogenic effects[93]	Inhibit platelet function[74]	None found
Trigonella foenum-graecum (fenugreek)	1 (P-1)	None found	Possible reduction in platelet activity possibly leading to excess bleeding in patients with bone marrow suppression[75]	None found
Triticum L.spp aestivum (wheatgrass)	2 (I-2)	None found	None found	None found
Urtica dioica L./urtica urens(stinging nettle)	42 (T-42)	None found	May ameliorate cisplatin-induced toxicity in mice[82]	None found
Valeriana officinalis L. (valerian)	1 (L-1)	None found	Not found	None found
Vitis vinifera (raisin)	1 (T-1)	In vitro CYP3A4 inhibition possibly causing increased toxicity of etoposide, paclitaxel, vinblastine, vincristine, and cyclophosphamide[47]	In vitro evidence suggests decrease of platelet aggregation[76]	None found
Viscum album L. (mistletoe)	4 (I-3, T-1)	None found	Systematic review reported one serious adverse event related to viscum; mild adverse events were local reactions at injection site;allergic reactions were rare[81]	Potential synergism of viscum album lectins with paclitaxel[91]
Vitex negundo	1 (U-1)	None found	Not found	None found
Zingiber officinale (ginger)	8 (C-1, I-3, L-1, P-2, T-1)	None found	May inhibit thromboxane synthetase and decrease platelet aggregation[75]	None found

Abbreviations: EGCG, Epigallocatechin gallate; HCPs, health care practitioners; OATP, organic anion-transporting polypeptide.
[a] As identified by the study oncology HCPsfrom the following countries: C indicates Cyprus; E, Egypt;I, Israel;J, Jordan; L, Lebanon; P, Palestinian Authority;Q, Qatar;T, Turkey; U, United Arab Emirates; Y, Yemen.

anticoagulant activity.[95] Herbal products with hepatotoxic effects included *Nerium oleander*[79] and ginseng in patients treated with imatinib,[80] and localized allergic reactions were found with subcutaneously administered *Viscum album L*.[81] At the same time, several herbal products were shown to either prevent or reduce the toxicity of chemotherapy agents, such as *Urtica dioica L* attenuating cisplatin-related toxicities.[82]

Effects on Antitumor Activity

Several of the herbal products identified were found to induce and augment the cytotoxic activity of conventional anticancer agents. This results from either a synergistic interaction with the conventional drug or chemosensitization of the cancer cells. Increased cell death has been observed with *Curcuma longa L*. in patients with cisplatin-resistant lung cancer cells[83]; *Ganoderma lucidum* with doxorubicin in HeLa cells[84] and doxorubicin-resistant leukemic cell lines[85]; *Linum usitatissimum L*. enhancing the antitumor effects of trastuzumab in breast cancer cell lines[86]; *Nigella sativa L*. with gemcitabine and oxaliplatin in pancreatic cancer cells[87]; *Panax ginseng* metabolites (Rh2 ginsenosides) with paclitaxel in multidrug-resistant breast cancer cells[88]; *Silybum marianum L*. with doxorubicin-related apoptosis in the MCF-7 breast carcinoma cell line[89] as well as with etoposide and doxorubicin in drug-resistant smallcell lung carcinoma cells[90]; and finally, *Viscum album L*. with paclitaxel in human SK-hep1 hepatocarcinoma cells.[91] Herbal compounds also have been found to attenuate the anticancer effects of chemotherapy (eg, inhibition of etoposide on the MCF-7 breast cancer cells in the presence of curcumin)[92] and promote cancer progression (eg, *Thymus vulgaris* on estrogen receptor activity).[93]

DISCUSSION

There are many challenges facing Middle Eastern oncology HCPs treating patients with cancer. These professionals are working in a society in which CTM practices such as herbal medicine are an integral aspect of the local culture of health care. The research on this subject has been focused primarily on patient-HCP communication, which has improved significantly in recent years and reduced the Rubicon of "to tell or not to tell" that many patients have faced in the past.[94] Today's oncology HCPs are expected to provide evidence-based guidance for the use of herbal products during anticancer treatments.[95]

In the current study, oncology HCPs were asked about the herbal products most frequently used by their patients and about their own perspectives regarding the integration of CTM in supportive cancer care. However, they were not asked about their role in prescribing the herbal agents themselves. Earlier research concerning the role of HCPs in prescribing herbal medicine to their patients was conducted in an integrative setting in which a CTM-trained physician consulted patients on this practice.[4] In the overwhelming majority of cases, patients were found to have initiated the use of herbal products on their own, as part of their CTM treatment. Although the role of oncology HCPs in advising patients on the use of herbals needs to be studied more in depth, it is our impression that most herbal medicine use is patient-derived, especially in cases in which there is no professional oncology consultant available to advise which products should be used (or avoided).

Communication between patients and oncology HCPs is a 3-armed triangle, representing the patient, the oncology HCP, and the integrative physician (IP). IPs are physicians with training in herbal medicine, and can serve as an important resource for both patients and their HCPs, providing up-to-date and evidence-based information regarding the effectiveness and safety of herbal medicine. The IP consultation should be patient-centered, taking into consideration the many aspects of the patient's health belief model and expectations. IPs should be aware that such a patient-centered consultation, especially in cross-cultural regions such as the Middle East, needs to address not only the individual's perspective. The IP consultation needs to understand the broader sociocultural and religious context of the patient's, and the HCP's, community, as well as their affinity with traditional medicine. We found a higher rate of reported herbal use among Muslim respondents, which may suggest that the dialogue between the HCP, patient, and IP may also relate to communication aspects of care. This may reflect the individualistic and collective cultural perspectives that can often influence decision-making. IPs should be clinically focused, helping to reduce the side effects of treatment and improve quality of life. This will enable patients and their HCPs to reach an informed decision regarding their use of herbal products while keeping within the guiding principle of primum non nocere (first, do no harm).

In the current study, 29 of the 44 herbal products identified were found to be associated with safety-related concerns. These included herb-drug interactions, toxic effects of the herbal components, and alterations in the response of cancer cells to chemotherapy either through synergy or increased chemosensitivity.[96] Changes to the CYP, P-glycoprotein, or other metabolic pathways can either reduce the bioavailabilty of drugs (with decreased

efficacy) or, conversely, increase serum levels (with increased toxicity). With regard to the potential for an increased response of cancer cells to anticancer treatments, this may appear to be desirable. However, if proven true, then adjustments in the dose density of chemotherapy and other anticancer therapies need to be made. Unnecessarily intense dose-dense therapies inevitably result in an increased risk of toxicity, which should be avoided if possible.

The majority of the findings regarding herb-drug interactions, including those found for the 29 herbal productsidentified herein, are based on either preclinical or small clinical trials. These include case reports, postmarketing surveillance studies, or reports with indirect findings from explanatory (phases 1-3) clinical research. This makes it extremely difficult to reach an evidence-based conclusion on their use in order for patients and their oncology HCPs to make an informed and responsible decision. The "easy" solution for this would indeed be to make an across-the-board recommendation against the use of any and all herbal products during active anticancer treatment. However, such a negative and critical approach can increase nondisclosure of this practice among patients, especially in societies in which herbal medicine use is part of the traditional health-related culture.

A more reasonable and practical approach is to educate oncology HCPs about CTM and herbal medicine use, providing them with the tools for better communication with their patients. All herbal medicinal products being used should be recorded in the medical file, and patients should be referred to a qualified IP for guidance. The consultation should be part of the conventional oncology service, and patients should be asked specifically about their use of herbal medicine, as well as about their expectations from this treatment. The use of herbal products for which there is no evidence of effectiveness, or for which there are significant safety concerns, should be discouraged.

In the current study, we addressed several issues that were related to the safety of herbal medicine use during chemotherapy. These included the potential for herb-drug interactions, which may compromise efficacy and increase the toxicity of anticancer treatments. The same is true for conventional drugs, which are frequently being used in supportive care and also may interact negatively with anticancer treatment. An example of this is the interaction between tamoxifen and CYP-2D6 inhibitors such as selective serotonin reuptake inhibitors, which are used for the treatment of depression and hot flashes.[97] The use of such conventional drugs in conjunction with anticancer agents can also lead to reduced efficacy and increased toxicity.[98] The potential for drug-drug interactions should be addressed in clinical practice with the same rigor and thoroughness asis required when investigating herb-drug interactions.

The current study has several limitations, reflecting the complex geographic, economic, and political character of the MiddleEast. This collaborative research program took place at a time of intense conflict in the region, requiring the creation of a unique methodological design. In contrast to most of the research regarding CTM and herbal agents, which is based almost exclusively on patient-reported data, we decided to target conventional oncology HCPs who were working in a conventional cancer treatment setting.[99,100] This allowed us to avoid several patient-based biases, such as a reporting bias resulting from nondisclosure of CTM use to researchers who patients may have believed had a negative attitude regarding nonconventional medical approaches.[101] For this purpose, we asked oncology HCPs to provide a list of herbal products being used by their patients with cancer, using a snowball sample approach among participants in an MECC workshop program.[28] This may have led to a selection bias because the workshop was attended by HCPs who are oriented to supportive care and thus more open to the integration of CTM into cancer care. At the same time, it is likely that some HCPs did not participate in the study for fear of professional or personal consequences. In addition, the list of herbal medicines identified by the study HCPs was not compared with what patients may have reported had they been asked.

The absence of a validation process for the questionnaire used in the currentstudy needs to be addressed in future research. This questionnaire was designed based on insights gleaned from an HCP focus group, as well as from a previous validated patient-oriented questionnaire that had been administered to patients with cancer in Israel and the Palestinian Authority.[34,35] The use of CTM was based solely on the reports of oncology HCPs and not on those of their patients. As such, we could not explore any associations between the prevalence of herbal medicine use and demographic factors such as socioeconomic conditions or patients' motives to use herbal medicines (eg, CTM use as a more affordable treatment option). Nevertheless, we did not find any correlation between national rates of herbal medicine use and economic status. Indeed, a high rate of herbal medicine use was reported both in wealthy countries such as Qatar and the United Arab Emirates as well as in less affluent countries such as the Palestinian Authority and Lebanon.

Future research will need to further explore these aspects of CTM use in Middle Eastern countries. This should be done by conducting a regional patient-centered survey, comparing patients' perspectives regarding the integration of CTM in supportive cancer care in varied oncology settings across the Middle East. This approach could provide further insight into patients' perspectives, which were not explored in the current study, such as the extent to which patients demand that CTM be part of their care; whether the use of herbal medicine is CTM-based or influenced by the increased interest in cancer-related complementary medicine practice in Western societies; the association between CTM use and cost-related issues; the variations in treatment options based on the type of cancer; specific issues related to quality of life; and finally, the incorporation of herbal medicine into the palliative care setting, in which therapeutic options are often limited. Despite the above limitations, the study methodology reflects an important and objective approach for describing a general trend of herbal medicine use by patients with cancer in Middle Eastern countries. Future research will need to address these limitations, as well as assess the impact of integrating IP consultations within the conventional oncology setting, with the provision of guidance regarding the use of herbal medicine in supportive cancer care. Such an approach is important to bridge the physician-patient communication gap, providing patients and their oncology HCPs with important information regardingthe safe and effective use of herbal medicine.

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CONFLICT OF INTEREST DISCLOSURES

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