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Complementary and alternative medicine use among cancer patients in Palestine with special reference to safety-related concerns

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ABSTRACT

Ethnopharmacological relevance: The use of CAM including herbal medicine as the most preferred CAM modality, among cancer patients who are taking prescription medications has shown to be highly prevalent worldwide as well as in several Middle Eastern countries, with a high percentage of the patients do not disclose their CAM use to treating physician.

Aim of the study: The current study aimed to evaluate the patterns of CAM use among two cohorts of cancer patients in Palestine over a three-year period, and to identify socio-demographic factors that are associated with CAM use.

Materials and methods: Across-sectional survey of patients attending outpatient cancer clinics. The method was based on a semi-structured questionnaire. In order to identify safety-related concerns associated with the products listed, a literature search was conducted using different databases (PubMed, Micromedex, AltMedDex, and the Natural Medicine Comprehensive Database).

Results: In 472 cancer patients including 372 of the 2011 cohort; and 100 of the 2014 cohort, the overall prevalence of CAM use was 69.5%. CAM users were more likely to be $\leq$65 years old, village resident, being in the midst of chemotherapy, to have high interest spiritual quest, and to have no other chronic diseases. A significant number of CAM users reported using herbal preparations (98.3%, and 89.6% in the two study cohorts, respectively). In the current study, a total of 40 plant taxa belonging to 23 botanical families were reported by $\geq$3 cancer patients in the two cohort groups. The top most commonly used plant in the 2011 cohort group was *Arum palaestinum* (43.5%), while *Ephedra foeminea* emerged as the top most commonly utilized plant (from 0.0% in 2011 to 55.2% in the 2014 cohort), mainly due to a recent publicizing and portraying of the plant in the local media as an effective cancer herbal remedy. Safety-related concerns were associated with 33 (82.5%) herbs, including herb-drug interactions with altered pharmacokinetics (8, 20% herbs), direct toxic effects (16, 40% herbs), and increased in vitro response of cancer cells to chemotherapy (30, 75% herbs).

Conclusions: CAM use, especially herbal medicine in cancer is highly prevalent in Palestine. This study has demonstrated the role of the media on the emergence of new CAM herbal therapies among cancer patients in Palestine, and discussed its potential implications on patients and for oncologists who are treating them. Some of the most widely used herbal medicines by cancer patients in the present work are known to interact with conventional anticancer drugs. Hence, the disclosure of the use of herbal remedies by patients to health professionals with sufficient training in CAM use is important for the later in order to assess whether there are any possible herbal drug interactions and/or harmful drug reactions.

1. Introduction

Cancer is an important public health challenge in Palestine and worldwide (Palestinian Health Information Center, PHIC, 2015; Ferlay et al., 2015). In Palestine, cancer incidence rate was 82.2 per 100,000 of the population in 2014 (PHIC, 2015). After

Abbreviations: PHIC, Palestinian Health Information Center; CAM, Complementary and alternative medicine; CYP, Cytochrome P450; TAPHM, Traditional Arabic Palestinian Herbal Medicine; IRB, Institutional Review Board; BERC, Biodiversity and Environmental Research Center; EF, *Ephedra foeminea*; EGCG, Epigallocatechin gallate; OATP, Organic anion transporting polypeptides; TRAS, Trastuzumab

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cardiovascular diseases (29.5%), cancer was the second most frequent cause of death in Palestine (14.2%) (PHIC, 2015).

The term "complementary and alternative medicine" is used to describe those therapies that are considered to be complementary or alternative to "western" pharmaceuticals and medical practices, natural, or traditional medicine (Pearson and Chesney, 2007). The use of CAM among cancer patients who are taking prescription medications has shown to be highly prevalent worldwide (Ernst and Cassileth, 1998; Leng and Gany , 2014; Tuna et al., 2013; Farooqui et al., 2015; Molassiotis et al., 2006; Ezeome and Anarado, 2007; Sewitch and Rajput, 2010; Can et al., 2009; Davis et al., 2012) as well as in several middle eastern countries, e.g., Jordan (about 100%) (Akhu-Zaheya and Alkhasawneh, 2012), Saudi Arabia (90%) (Jazieh et al., 2012), Turkey (57%) (Yildiz et al., 2013), Israel (51%) (Paltiel et al., 2001), Morocco (46%) (Brahmi et al., 2011), and Iran (35%) (Montazeri et al., 2007). Between 20% and 70% of patients using CAM, including herbal therapies, do not inform their physician about using CAM as a result from an expected negative response (Davis et al., 2012). A similar trend was also found amongst other chronic diseases patients (e.g., diabetes, and hypertension) in Palestine (Ali-Shtayeh et al., 2012, 2013). However, many oncology health care providers admit their lack of competence in the field of herbal medicine (Trimborn et al., 2013).

In Palestine, as well as in many countries including Jordan, Turkey, and USA, several population-based studies, have shown extensive use of medicinal plants use as the most favored CAM modality (Ali-Shtayeh et al., 2011, 2012, 2013; Afifi et al., 2010; Akyol and Öz, 2011; Grover et al., 2002; Ezeome and Anarado, 2007; Gratus et al., 2009; Algier et al., 2005; Ali-Shtayeh et al., 2000). Herbal medicine contains pharmacologically active components, some of which might interact with conventional drugs (Ernst, 2000) which, in turn, could threaten the health of patients (Ernst et al., 2006; Izzo and Ernst, 2009). When pharmaceutical drugs are simultaneously used with herbal therapies, interactions may decrease or increase the toxicological or pharmaceutical effects of either ingredient (Ernst, 2000; Hardy, 2008; De Smet, 2004; Zhang et al., 2009). A potential risk to human health could be the concurrent use of multiple conventional therapies and herbal medicines (Werneke et al., 2004).

Herb-drug interactions can take place at the pharmaceutical, pharmacodynamic, or pharmacokinetics levels (Beijnen and Schellens, 2004). Interactions at the pharmacokinetic level involve changes in the metabolic pathway (absorption, distribution, metabolism, or excretion) of the chemotherapeutic drug. At the level of metabolism of anticancer drugs, almost all pharmacokinetic interactions involve cytochrome P450 (CYP) metabolizing enzymes, of which CYP3A4 is the most important enzyme in the metabolism of chemotherapeutic drugs (Lau et al., 2013). This problem may be aggravated by the emergence of new herbal therapies with unknown toxicity.

Traditional Arabic Palestinian Herbal Medicine (TAPHM) is closely related to patients' health belief models and is an integral part of the socio-medical landscape among the Palestinian population (Ali-Shtayeh and Jamous, 2006; 2008; Ali-Shtayeh et al., 2014). Lower cost and acceptability of medicinal herbal use in Palestine, encourage patients to believe in their healing potentials (Ali-Shtayeh and Jamous, 2006; 2008).

In Palestine, little is known on the use of CAM by cancer patients. The current study aimed to evaluate the patterns of CAM use among two cohorts of cancer patients in Palestine over a three-year period. In addition, the study focused on the information-seeking behavior and CAM use disclosure to health professionals. The study was also aimed to identify demographic and socio-economic factors that are associated with CAM use. Another aim was to search the literature for potentially harmful herb-drug interactions. To our knowledge, no previously published study has investigated the pattern of CAM use among Palestinian patients living with cancer.

2. Methods

2.1. Subjects and recruitment

The study used a cross-sectional survey of patients attending the Tumors Outpatient Department at Alwattani Governmental Hospital in Nablus, in Palestine. To ensure a representative sample, the interviews were conducted on different days and at different times. The study included patients of both sexes across different age groups. Ethical approval was obtained prior to the study from the Institutional Review Board (IRB) at the Ministry of Health in Nablus. The interviews were carried out by researchers from the Biodiversity and Environmental Research Center (BERC), Nablus. Prior to proceeding with the interview, the patients were informed about the purpose of this study and confirmed that all information would remain confidential and be used for research purposes only. If the patients were younger than 16 years of age or unable to interact, the next of kin were interviewed.

2.2. Study questionnaire

The study patients were asked a series of questions regarding demographic details of the patient; disease details; information about use of CAM; source of information; purpose of the use of CAM and outcomes; extent of CAM therapy effect on the treatment of cancer; patients' objections or misgivings about seeking CAM for the treatment of patient's cancer, seeking out CAM if it were provided as part of the oncological service; consultation with healthcare professional about using CAM in the treatment of cancer; main expectations of CAM consultation and treatment integrated in the Tumors Outpatient Department; most troublesome problems which the patient would like to improve as a result of CAM treatment; phase in the oncological treatment was the patient at the time of the study; and extent of interest in spiritual or religious quest. The majority of the questions had pre-prepared answers, and the main themes addressed by the questionnaire are represented in Table 1. To evaluate the questionnaire, a pilot study was conducted with 50 randomly selected patients. The results from the pilot study have not been included in the analysis of data for this study.

2.3. Research cohorts

In this study, 472 patients diagnosed with cancer were randomly selected at the Tumors Outpatient Department, Alwattani Hospital, Nablus and participated in the study. The study took place on two periods, the first from April - July 2011 (2011 cohort group), and the second from Aug – Oct 2014 (2014 cohort group). A total of 372 patients, and 100 patients participated in the two periods, respectively.

2.4. Review of the literature on the risk of herb-drug interactions

An extensive review focusing on simultaneous use of CAM herbal medicine and conventional therapies in cancer care among Palestinian patients was performed. The search was based on various databases (PubMed, Google scholar, Micromedex, AltMedDex, and The Comprehensive Natural Databases published between January 2011 and Dec 2015 (Natural Medicines Comprehensive Database Home page, 2015)). The scientific and English common names of the identified herbs were used to carry out a Medical Subject Headings (MeSH) search. The search included the

Table 1
Main themes addressed by the study questionnaire.

1. Demographic details of the patient or next of kin if the patient is < 16 years of age	Gender, age group, marital status, education level, area of residence.
2. Disease details (obtained from patient file)	Having other chronic diseases: e.g., diabetes, hypertension, others. Duration of having cancer (in years). Having any other chronic diseases. Having other hypertensive members in the family. Current treatment (s) of the patient (drug, dose, time and frequency of use).
3. Information about CAM use	Complementary medicine treatments related to cancer Use of herbal plants for the treatment of cancer Plant part used, forms of preparation (raw, cooked, infusion, decoction, juice), mode of preparation, administration, dose, period of use Origin of the herbs (local, imported)
4. Source of information	Friends, family member, physician, pharmacist, herbalist, media (TV, radio, hardcopy, internet, advertisements, text messages, etc.)
5. Purpose of CAM use	Curing disease, slow down progress of disease, relief of symptoms, reducing medication side effects.
6. Outcomes	Did the patient achieve the sought effect? Did the patient discuss the CAM use with the physician? Did the patient experience any side effects from using herbal preparations, and what side effects he/she had experienced? Did your physician ask whether you use other alternative medicine (especially herbs) beside medication for the treatment of cancer?

following terms: herb-drug interaction, safety, adverse effects, toxic/toxicity, side effects, risk, absorption, bioavailability, synergism, induction, inhibition, and chemosensitization.

2.5. Data analysis

Cancer patients participated in the study were classified as either CAM users or non-users according to whether or not they used at least one CAM modality. Information on time of since diagnosis, stage of disease, and previous cancer treatments received by the patients were abstracted from their medical reports. We tested the association and correlation of CAM use with socio-demographic characteristics listed in Table 2. Comparisons between categorical groups were performed using Pearson's Chi-Square ($\chi 2$) or Fisher's Exact Tests, as appropriate. In all analyses, $P < 0.05$ was considered statistically significant. Analyses were conducted using the Statistical Package for Social Sciences (SPSS) program, version 17.

3. Results and discussion

This study is the first attempt to estimate the frequency of CAM use in the management of cancer and evaluate factors associated with such use, over a period of 3 years. The study was also motivated by the emergence of *Ephedra foeminea* (Alanda) in 2014 as widespread herbal therapy among Palestinian cancer patients.

3.1. Demographics

Table 2 summarizes the demographic characteristics of the participants. Of the 372 patients interviewed in the 2011 cohort group, 290 were females (78.0%) and 80 were males (22.0%) patients (2 missing) (Table 2). The majority of the interviewees were ≤ 65 years of age (74.2%). A large percentage of the individuals of the study population were married (75.3%), 23.1% had high school degrees, 15.6% achieved university degree level, and 60.8% were illiterate or had a primary educational level. Of the 100 patients interviewed in the 2014 cohort group, 89 were females (89%) and 11 were males (11%) (Table 2). The majority of the interviewees were ≤ 65 years of age (75%). A large percentage of the individuals of the study population were married (63%), 25% had high school degrees, 16% achieved university degree level, and 59% (n=59) were illiterate or had a primary educational level.

3.2. CAM modalities used by patients with cancer

This study revealed that cancer patients using CAM have used one or more CAM modality in the management of their disease. Of the 372 participants in the first cohort group, 62.4% (n=232) were CAM users, while of the 100 participants in the second cohort group, 96% were CAM users. However, the increase in CAM use in 2014 may be attributed to the increase in the use of other CAM types including the use of food supplements, excercise, and prayers. The high percentage of CAM use in this study, supporting the similar trend of CAM use throughout the world (Ernst and Cassileth, 1998; Farooqui et al., 2015; Molassiotis et al., 2006; Ezeome and Anarado, 2007; Sewitch, and Rajput, 2010; Can et al., 2009; Davis et al., 2012) as well as in other middle eastern countries, e.g., Jordan (about 100%) (Akhu-Zaheya and Alkhasawneh, 2012), Saudi Arabia (90%) (Jazieh et al., 2012), Turkey (57%) (Yildiz et al., 2013), Israel (51%) (Paltiel et al., 2001), Morocco (46%) (Brahmi et al., 2011), and Iran (35%) (Montazeri et al., 2007). The percentages obtained in this study regarding the use of CAM are comparable to those obtained in Palestine among hypertensive patients (85.7%) (Ali-Shtayeh et al., 2013).

Considering the types of CAM utilized by the cancer patients (Table 3), a significant number of patients in the 2011 cohort (98.3%) used herbal preparations. The other types of CAM used by the cancer patients included eating honey (64.7%), prayers and reading the holy books (19.4%), using animal products (17.7%), massage (5.2%) and others (vitamins and cupping). Considering the types of CAM utilized by the cancer patients in the 2014 cohort group, a significant number of patients (86/96, 89.6%) used herbal preparations. The other types of CAM used by the cancer patients included prayers and reading the holy books (85.4%), food supplements (62.5%), eating honey (66.7%), exercise and animal products (32.3%), and others including massage, relaxation, and cupping (Table 3). Based on the popularity of herbal medicine among Palestinians in the treatment of a large number of ailments and diseases, it was expected that the percentage of herbal medicines users will also be high amongst patients with cancer (≥ 90% in this study). Ease of accessibility, lower costs and social acceptability in the use of medicinal herbs in Palestine, as well as the long history and experience of traditional use of these herbs encourage patients to believe in their healing effects (Ali-Shtayeh and Jamous, 2006).

The percentages obtained in this study regarding the use of herbs are higher than those obtained in Palestine among breast cancer (68%) (Jaradat et al., 2016), diabetic (52%) (Ali-Shtayeh et al., 2012), or hypertensive patients (62.1%) (Ali-Shtayeh et al., 2013) and also higher than those reported in neighboring Jordan among hypertensive (7.6%) (Wazaify et al., 2013), cancer (35.5%) (Afifi et al., 2010), or diabetic patients (16.6%) (Wazaify et al., 2011). The differences in the rate of herbal medicines use between these studies may be attributed to differences in definitions of CAM, the research methodology used, cultural, geographical or socio-economic variables, all of which can influence an individual's decision whether to use herbal medicines (Afifi et al., 2010).

Due to limitations with conventional anti-cancer therapies, including their accessibility, efficacy, cost and adverse effects,

Table 2
Demographic characteristics of the study participants. Relative percentage of CAM users and non-users at each cohort group and in each socio-demographic category were calculated from the total number of respondents at category.

Item	CAM Users 2011 Cohort Group				*p value**	CAM Users 2014 Cohort Group				*p value**
	No		Yes			No		Yes		
	n	%	n	%		n	%	N	%	
Age	**N=372**				< 0.001	**N=100**				**0.26**
≤65	88	**23.7**	188	**50.5**		**2**	**2.0**	**73**	**73.0**	
>65	52	**14.0**	44	**11.8**		**2**	**2.0**	**23**	**23.0**	
Gender	**N=370**[a]				**0.009**	**N-100**				**0.473**
Male	36	**9.7**	44	**11.9**		0	**0.0**	11	**11.0**	
Female	103	**27.8**	187	**50.5**		4	**4.0**	85	**85.0**	
Residence	**N=372**				**0.002**	**N=100**				**0.707**
City	70	**18.8**	102	**27.4**		2	**2.0**	32	**32.0**	
Village	54	**14.5**	122	**32.8**		2	**2.0**	56	**56.0**	
Refugee camp	16	**4.3**	8	**2.2**		0	**0.0**	8	**8.0**	
Marital Status	**N=370**[a]				**0.704**	**N=100**				**0.441**
Single	25	**6.8**	33	**8.9**		0	**0.0**	14	**14.0**	
Married	106	**28.6**	174	**47.0**		2	**2.0**	61	**61.0**	
Divorced	2	**0.5**	4	**1.1**		0	**0.0**	3	**3.0**	
Widowed	6	**1.6**	20	**5.4**		2	**2.0**	18	**18.0**	
Number of children	**N=358**[a]				**0.027**	**N=99**[a]				**0.001**
0	25	**7.0**	49	**13.7**		0	**0.0**	20	**20.2**	
1	4	**1.1**	8	**2.2**		1	**1.0**	4	**4.0**	
2	4	**1.1**	14	**3.9**		1	**1.0**	4	**4.0**	
3	16	**4.5**	10	**2.8**		0	**0.0**	8	**8.1**	
>3	88	**24.6**	140	**39.1**		2	**2.0**	59	**59.6**	
Education	**N=370**[a]				**0.07**	**N=100**				**0.457**
Illiterate	46	**12.4**	46	**12.4**		0	**0.0**	19	**19.0**	
Primary school	45	**12.2**	89	**24.1**		2	**2.0**	38	**38.0**	
High school	28	**7.6**	58	**15.7**		2	**2.0**	23	**23.0**	
Higher education	20	**5.4**	38	**10.3**		0	**0.0**	16	**16.0**	
Employment	**N=370**[a]				**0.062**	**N=100**				**0.454**
No change	20	**5.4**	28	**7.6**		4	**4.0**	43	**43.0**	
I work but less	22	**5.9**	32	**8.6**		0	**0.0**	16	**16.0**	
I stopped working	32	**8.6**	44	**11.9**		0	**0.0**	13	**13.0**	
I didn't work before I'm not working now	57	**15.4**	113	**30.5**		0	**0.0**	6	**6.0**	
I work more today than before	2	**0.5**	0	**0.0**		0	**0.0**	1	**1.0**	
other	6	**1.6**	14	**3.8**		0	**0.0**	17	**17.0**	
Oncological phase	**N=370**[a]				**0.006**	**N=100**				**0.959**
Before chemotherapy	9	**2.4**	1	**0.3**		0	**0.0**	3	**3.0**	
In the midst of chemotherapy	122	**33.0**	216	**58.4**		3	**3.0**	51	**51.0**	
I had chemotherapy up until 6 month ago	2	**0.5**	4	**1.1**		0	**0.0**	9	**9.0**	
In the midst of radiotherapy	0	**0.0**	0	**0.0**		0	**0.0**	1	**1.0**	
under surveillance only	2	**0.5**	10	**2.7**		1	**1.0**	29	**29.0**	
other	4	**1.1**	0	**0.0**		0	**0.0**	3	**3.0**	
Cancer types	**N=364**[a]				**0.01**	**N=100**				**0.915**
Breast	47	**12.9**	121	**33.2**		4	**4.0**	66	**66.0**	
Uterus/cervix/ovary/vagina	8	**2.2**	16	**4.4**		0	**0.0**	4	**4.0**	
GIT (Gasrto intestinal, Colon)	30	**8.2**	50	**13.7**		0	**0.0**	14	**14.0**	
Respiratory	6	**1.6**	6	**1.6**		0	**0.0**	3	**3.0**	
Brain/neurology	8	**2.2**	0	**0.0**		0	**0.0**	1	**1.0**	
Thyroid	2	**0.5**	0	**0.0**		0	**0.0**	0	**0.0**	
Bone	4	**1.1**	2	**0.5**		0	**0.0**	2	**2.0**	
Hematopoelic/lymphoma	8	**2.2**	6	**1.6**		0	**0.0**	0	**0.0**	
Other (including testis/prostate/kidney/bladder)	24	**6.6**	26	**7.1**		0	**0.0**	9	**9.0**	
Spiritual quest	**N=368**[a]				**0.03**	**N=98**[a]				**0.002**
Very low interest	4	**1.1**	0	**0.0**		0	**0.0**	1	**1.0**	
Low interest	4	**1.1**	4	**1.1**		1	**1.0**	1	**1.0**	
Quit low interest	2	**0.5**	2	**0.5**		0	**0.0**	0	**0.0**	
Average interest	26	**7.1**	34	**9.2**		1	**1.0**	10	**10.2**	
Quit high interest	22	**6.0**	30	**8.2**		0	**0.0**	0	**0.0**	
High interest	77	**20.9**	133	**36.1**		0	**0.0**	10	**10.2**	
Very high interest	2	**0.5**	28	**7.6**		1	**1.0**	73	**74.5**	
Spiritual supporter	**N=368**[a]				**0.05**	**N=98**[a]				**0.683**
No	101	**27.4**	142	**38.6**		1	**2.3**	43	**97.7**	
Yes	37	**10.1**	88	**23.9**		2	**3.7**	52	**96.3**	
Chronic diseases	**N=372**				**0.012**	**N=100**				**0.527**
Chronic	50	**13.4**	56	**15.1**		2	**2.0**	38	**38.0**	
No chronic	90	**24.2**	176	**47.3**		2	**2.0**	58	**58.0**	
Cancer recurrence	**N=372**				**0.163**	**N=100**				**0.597**
No	122	**32.8**	192	**51.6**		3	**3.0**	77	**77.0**	
Yes	18	**4.8**	40	**10.8**		1	**1.0**	19	**19.0**	

* p value was determined by chi-square.
[a] Numbers do not add up to the total population size, as some data were missing.

Table 3
Types of CAM utilized by patients with cancer in the two studies.

CAM category	Specific CAM treatment	CAM Users 2011 Cohort Group		CAM Users 2014 Cohort Group	
		Num. of CAM users	%	Num. of CAM users	%
Total Cam Users and %		232	**62.4**	96	**96.0**
Biological based therapies	Herbs	228	**98.3**	86	**89.6**
	Honey	150	**64.7**	64	**66.7**
	Animal product*	41	**17.7**	31	**32.3**
	Food supplements	14	**6.0**	60	**62.5**
	Kefir grain or Indian mushroom	9	**3.9**	4	**4.2**
Manipulative & body based therapies	Exercise	–	**0.0**	31	**32.3**
	Massage	12	**5.2**	9	**9.4**
	Relaxation	6	**2.6**	3	**3.1**
Mind/body interaction	Prayers, reading holy book, Zamzum water	45	**19.4**	82	**85.4**
Traditional oriental medicines	Cupping	3	**1.3**	1	**1.04**

* Goat milk, camel milk, ostrich fat and chicken liver

Palestinian cancer patients have obviously turned to CAM, in search for a treatment with potential efficacy and few adverse effects (Munshi et al., 2008). However, the popularity of CAM indicates the patients' preference towards integrative approach to cancer management.

3.3. Factors associated with CAM use among cancer patients

The CAM users in the 2011 cohort group consisted predominantly of females (n=187, 50.5%). The relationship between CAM use and respondents' demographic status is shown in Table 2. CAM users were more likely to be $\leq$65 years old (50.5%), village resident (32.8%), to have family size of $>$3 children (39.1%), oncological phase, being in the midst of chemotherapy (58.4%), to have breast or GIT cancer (47%), to have high interest spiritual quest (36.1%), and to have no other chronic diseases (47.3%). A statistically significant association was identified between the users and non-users in age ($\leq$65 years old use $>$ older than 65 years old) (p=0.000), to have a small to medium family size (small to medium family size $>$ larger family size) (p=0.027), and having no other chronic diseases (patients having no other chronic diseases use CAM more) (p=0.012). No statistically significant association was identified between the users and non-users of CAM in marital status (p=0.704), educational level (p=0.070), employment (p=0.062), having a spiritual supporter (p=0.05), and cancer recurrence (p=0.163). The examination of medical files and interviews found that all the cancer CAM users had used CAM with prescribed medications (Table 2). In contrast to other studies (Johansen and Toverud, 2006; Werneke et al., 2006) where well-educated and wealthy patients were more likely to consume herbal products as CAM than less educated patients, less educated patients were found to be more likely to utilize herbal products than the well-educated patients.

The CAM users in the 2014 cohort group consisted predominantly of females (85%). The relationship between CAM use and respondents' demographic status is similar, though not significant in most cases, to that in the 2011 cohort group (Table 2). This might be attributed to the small size of the population study in 2014. The examination of medical files and interviews found that all the cancer CAM users had used CAM with prescribed medications (Table 2).

Table 4
Pattern of use of CAM by cancer patients (n=232, and 96, in 2011 cohort group and 2014 cohort group, respectively).

Characteristic	CAM Users 2011 Cohort Group		CAM Users 2014 Cohort Group	
	Number of patients[a]	%	Number of patients[b]	%
Did the patient discuss the CAM use with the physician*				
Yes	66	28.45	37	38.5
No	156	67.24	59	61.5
Did the patient achieve the sought effect?				
Yes	162	69.83	66	68.8
No	50	21.55	11	11.5
Don't know	20	8.62	19	19.8
Origin of the herbs				
Imported	2	0.8	1	1.0
Local	228	96.2	74	77.1
Local and imported	6	2.5	11	11.5
Purpose of CAM use				
Curing disease	188	79.3	37	38.5
Others	119	50.2	1	1.0
Reducing medication side effects	8	3.4	2	2.1
Relief of symptoms	102	43.0	1	1.0
Slowdown of progress of disease	64	27.0	5	5.2
Source of information				
Doctor	**12**	5.1	7	7.3
Family	**132**	55.7	23	24.0
Friends	**172**	72.6	54	56.3
Herbalist	**8**	3.4	1	1.0
Media	**76**	32.1	67	69.8
Form of preparation				
Cooked	204	23.1	84	13.4
Decoction	351	39.8	217	34.7
Fresh	69	7.8	102	16.3
Juice	37	4.2	59	9.4
Oil	0.0	0.0	79	12.6
Raw	221	25.1	85	13.6
Effect of CAM use				
Affected it very badly	0	0.0	1	1.0
Affected it quite badly	0	0.0	0	0.0
Had no effect	44	18.6	9	9.4
Affected it quite well	64	27.0	27	28.1
Affected it very well	78	32.9	59	61.5
Hesitation				
Yes	24	10.34	10	10.4
No	205	88.36	84	87.5
Don't know	2	1.29	2	2.1
Seeking CAM				
Yes	211	90.95	85	88.5
No	12	5.17	8	8.3
Don't know	9	3.88	3	3.1

* Numbers do not add up to the total population size, as some data were missing.
[a] The total number here was more than 237, because some participants reported more than one choice.
[b] The total number here was more than 96, because some participants reported more than one choice.

3.4. Pattern of herbal preparation use among participants

The majority of cancer CAM users using herbal preparations in the two cohort groups obtained their supply from Palestine (96.2%, and 77.1% in the 2011, and 2014 cohort groups respectively). This also highlights the availability and acceptability of herbal therapies among the population. Cancer CAM users in this study preferred to use the herbs mainly in a decoction form (39.8%, 34.7%), and raw (7.8%, 16.3) (Table 4) in the two cohort groups respectively.

A disturbing result was that most patients (about 62–67%) had never disclosed the use of herbal remedies as CAM to their health care providers (e.g., physician or pharmacist), and physicians had

not routinely asked about such use. As a result, serious herb-drug interactions may be missed. This finding is in agreement with the previous studies in Palestine (Ali-Shtayeh et al., 2010, 2011, 2012) and worldwide (Davis et al., 2012) where comparable numbers of patients had not disclosed it to their health professionals. This indicates a lack of patient awareness of the dangers that may accompany the unsupervised use of medications and or herbs concurrently. It also raises questions regarding whether health professionals sufficiently explore their patients self-use of other forms of treatment. The self-administration of herbs use in conjunction with conventional medicines without disclosure of herbal remedies use to health care professionals may result in ineffective cancer management and adverse treatment side-effects (Chavez et al., 2006; Chang et al., 2007).

Different reports indicated that potentially serious interactions exist between some of the reported herbal medicines by cancer patients in the present work, e.g *Camellia sinensis, Curcuma longa, Foeniculum vulgare, Matricaria aurea, Sesamum indicum, Allium sativum, and Tamarindus indica* and widely used conventional pharmaceuticals (Appiah-Opong et al., 2007; Saleh et al., 2012; Meijerman et al., 2006; Piscitelli et al., 2002; Golden et al., 2009; Roth et al., 2011; Lim et al., 2012). Hence, the disclosure of the use of herbal remedies by patients to health professionals is important for the later in order to assess patient needs, compliance, efficacy of herbal remedies, and more importantly whether there are any potential drug interactions and adverse drug reactions (Tachjian at al., 2010; Hasan et al., 2009). Potentially serious consequences might be avoided by obtaining a more careful history about CAM use. Thus it is strongly recommended that, information on the use of herbal remedies as CAM be incorporated into clinical practice as well as patient and professional education, i.e., be incorporated into medical and health sciences curriculum (Tachjian et al., 2010; Izzo et al., 2005; Chang et al., 2007).

3.5. Sources of influence and perceived effects of CAM

The main sources of recommendations for herbal products in the 2011 cohort group were from friends (72.6%) and family (55.7%), followed by the media (32.1%), physician (5.1%), and herbalists (3.4%) (Fig. 1). About 79.3% of herbal medicine users (n = 188) believed that the herbal preparations would play role of curing the disease. Other reasons included relieving symptoms of the disease (43.0%), slowing down the progression of their disease (27.0%). The majority of herbal medicines users (69.83%) claimed to have obtained the sought effect from taking these herbs; however the majority of them (n = 156, 67.24%) did not report this fact to their health providers (Table 4).

The main sources of recommendations for herbal products in the 2014 cohort group were from media (77.9%) and friends (62.8%) followed by family (26.7%), physician (8.1%), and herbalists (1.2%) (Fig. 1). Thirty seven (38.5% of herbal medicine) users believed that the herbal preparations would play the role of curing the disease. Other reasons included relieving symptoms of the disease (1%), slowing down the progression of their disease (5.2%). The majority of herbal medicines users (68.8%) claimed to have obtained the sought effect from taking these herbs; however the majority of them (61.5%) did not report this fact to their health providers (Table 4). Most CAM herbal medicine users (68.8–69.83%) were satisfied with the perceived effect; a result consistent with previously recorded trends in Palestine among hypertensive (62.9%) (Ali-Shtayeh et al., 2013) and diabetic patients (71.7%) (Ali-Shtayeh et al., 2012).

The percentage of recommendations of herbal products in both cohort groups adds up to > 100%, this can be attributed to the fact that most patients recorded more than one source of recommendation for herbal products.

3.6. Herbs used as CAM in patients with cancer in Palestine

In Palestine, it is reported that a vast majority of the population still uses herbal medicine, indicating a deep rooted belief in the healing potential of plants (Ali-Shtayeh and Jamous, 2006, 2008). Several population-based studies, have demonstrated widespread use of herbal medicine as the most preferred CAM modality (Ali-Shtayeh et al., 2013; 2012). In the 2011 cohort group, 32 plant taxa belonging to 20 botanical families were reported by ≥ 3 cancer patients, with Lamiaceae (5 species), Apiaceae (4 species), and Fabaceae and Rosaceae (3 species each) being the most common (Table 5). While, 24 plant taxa, belonging to 17 botanical families, were cited by ≥ 3 of cancer patients in the 2014 cohort group, with Apiaceae (6 species), Lamiaceae (5 species), and Zingiberaceae (2 species) being the most common (Table 5). In the present study the most common herbal products consumed by the cancer patients in the 2011 cohort, included *Arum palaestinum* (43.5%), *Nigella sativa* (34.9%), *Phoenix dactylifera* (12.1%), *Matricaria aurea* (21, 9%), *Zingiber officinale* (19, 8.2%), whereas it included *Ephedra foeminea* (55.2%), *Punica granatum* (35.4%), *Phoenix dactylifera* (32.3%), *Nigella sativa* (30.2%), and *Arum palaestinum* (22.9%) in the 2014 cohort.

The number of herbs used by cancer patients (≥ 3) in the present work (32–24 species reported by 3 participants or above)

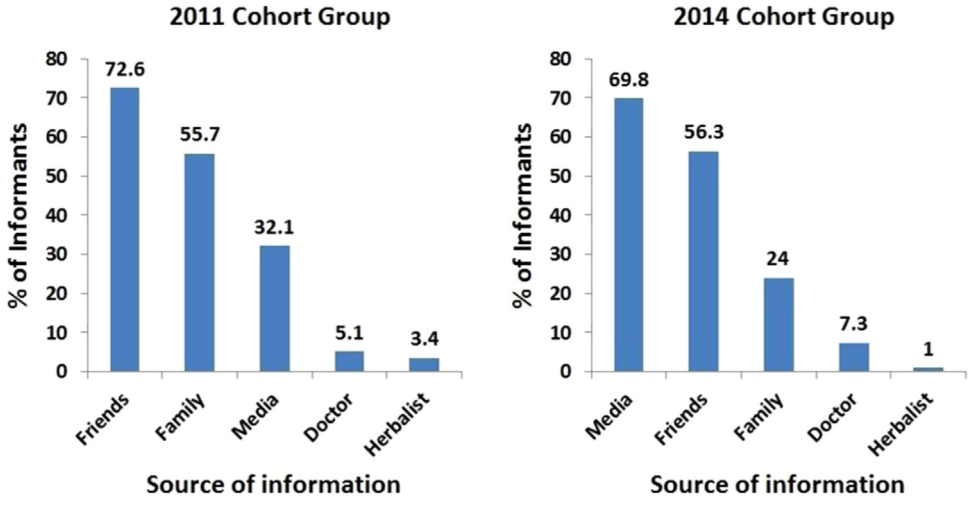

Fig. 1. Sources of information of herbal CAM use.

Table 5
List of plants used by cancer patients in this study: scientific name (family); English name; local name (Arabic); parts used; form of preparation; mode of preparation; administration, number of informants (%) in 211 cohort group; number of informants (% in 214 cohort group).

Botanical name (Family)	English common name	Arabic name	Part Plant used	Form of preparation	Mode of preparation	Administration	2011 Cohort group	2014 Cohort group
Allium cepa L.(Liliaceae)	Onions	بصل	Bulb, Leaves	Fresh, Cooked	Added to salad or eaten raw with olive oil Cooked with arum and olive oil Dip a piece of onion in honey Prepare onions with lemon juice	Eaten daily until recovery, olive oil can be added. 1teaspoon daily before breakfast 1 cup daily	5 (2.2%)	4 (4.2 %)
Allium sativum L. (Liliaceae)	Garlic	ثوم	Gloves	Fresh	Fresh	Eat 1-2 Clove garlic daily before breakfast until recovery	10 (4.3%)	2 (2.1%)
Amygdalus communis L. (Rosaceae)	Almond	لوز	Seeds	Raw	Dried seeds are eaten or mixed with honey	7 seeds daily until recovery, or 1 teaspoon twice a day with Honey		13 (13.5%)
Amygdalus Korschinskii Hand-Mazz (Rosaceae	Bitter almond	لوز مر	Seeds	Raw	Raw	Eating 6-7 bitter almond daily before breakfast	3 (1.3%)	
*Pimpinella anisum*L. (Apiaceae)	Anise	ينسون	Seeds	Decoction	A decoction is prepared by adding 1 teaspoon to two cups of boiled water. A decoction is prepared from the seeds with fenugreek, anise, nigella and fennel.	1-2 cups daily until recovery	12 (5.2%)	19 (19.8%)
Arum palaestinum Boiss. (Araceae)	Palestinian Arum	لوف فلسطيني	Leaves	Capsules, Decoction, Cooked	Leaves are dried and filled in a capsule Leaves are boiled in water Cooked with onions and olive oil Cooked with tomato, onions and wheat flower A decoction is prepared from the dried leaves by boiling in 2 liters of water	3-4 capsules daily before breakfast 1 cup in the morning Eat once daily 1-2 times a week 3 cups daily until recovery	101 (43.5%)	22 (22.9%)
Camellia sinensis Link. (Theaceae)	Tea	شاي أخضر	Leaves	Decoction	A decoction is prepared by adding 1 teaspoon of the plant to a cup of water	3 cups daily until recovery	2 (0.9%)	7 (7.3%)
Cassia senna L. (Fabaceae)	Senna	سنمكة، عشرق	Leaves	Decoction	A decoction is prepared from the plants	2 cups daily until recovery	5 (2.2%)	1(1.0%)
Citrullus colocynthis (L.) Schrader (Cucurbitaceae)	Colocynth	حنظل، التفاح المر، العلقم	Leaves	Decoction	A decoction is prepared from the plant	1 cup daily for a month	4 (1.7%)	
Citrus limon (L.) Burm. Fil (Rutaceae)	Lime, Limon Tree	ليمون	Fruits	Juice	A juice prepared from the fruits, sugar or honey can be added Eaten fresh	1/2 cup daily I fruit daily 3-4 times daily until	17 (7.3%)	5 (5.2%)

Botanical name (Family)	English common name	Arabic name	Part Plant used	Form of preparation	Mode of preparation	Administration	2011 Cohort group	2014 Cohort group
					A juice is prepared from 2 lemon fruits and 2 pomegranate in a liter of water, 7 teaspoons of sugar is added to the juice	Recovery		
Commiphora myrrha (Nees) Engl. (Burseraceae)	Cum Myrrh tree	المرة	The oleo-gum-resin from the stem	Raw	Raw	Swallow small piece daily before breakfast for one month	6 (2.6%)	1(1 %)
Coridothymus capitatus (L.) Reichb. (Lamiaceae)	Capitate Thyme	زعتر فارسي، زحيف	Leaves	Decoction	A decoction is prepared from the plant A decoction is prepared from a mix of sage, and thyme	1 cup daily until recovery 1-2 cups daily before breakfast	8 (3.4%)	2(2.1%)
Crataegus aronia (L) Bos. exDc. (Rosaceae)	Hawthorn	زعرور	Areal parts	Decoction	A decoction is prepared from the areal parts	1 cup is taken daily before breakfast as needed	4 (1.7%)	-
Cuminum cyminum L. (Apiaceae)	Cumin	كمون	Seeds	Decoction, Raw	Grinded seeds are eaten raw A decoction is prepared by adding 1 teaspoon of the seeds to a cup of boiled mint	Eat 1 teaspoon of grinded seeds 1 cup daily	-	5 (5.2%)
Curcuma longa L. (Zingiberaceae)	Turmeric	كركم	Roots	Decoction, Raw	1 teaspoon of the grinded roots is added to a decoction of Apple peel 1 teaspoon of the grinded roots is added to 1 teaspoon of honey Raw	1 cup daily until recovery 1 teaspoon daily before breakfast until recovery	-	13 (13.5%)
Daucus carota L. (Apiaceae)	Carrot	جزر	Roots	Fresh	Juice, fresh or boil the roots in water Fresh juice is prepared from carrot and apple a juice is prepared from carrot and lemon Mix a cup of carrot juice with a teaspoon of ginger and honey	3 cups daily, eat 2-3 roots daily either fresh or boiled until recovery drink I cup of the juice 2-3 times daily 1 glass of juice taken daily drink 3 times daily before breakfast for a month	14(6.0%)	20 (20.8%)
Ephedra foeminea Forssk. (Ephedraceae)	Ephedra	علندة	Areal Parts	Decoction	Add 350 g of the plant for 7 L of water then boil for two hours. Save the filtrate in the refrigerator for use a decoction is prepared from the plants with rosemary in five cups of water	1/2 L is taken daily 2 cups daily until recovery	-	53 (55.2%)
Ferula assa-foetida L. *(*Apiaceae)	Asafetida	حلتيت	An oleogum-resin obtained	Raw, Decoction	Raw Boil the mix in milk	Swallow a small piece with Gum Myrrh Tree daily until recovery until recovery Drink cup before breakfast	6 (2.6%)	1 (1 %)

Botanical name (Family)	English common name	Arabic name	Part Plant used	Form of preparation	Mode of preparation	Administration	2011 Cohort group	2014 Cohort group
			By incision of root			For 2 weeks		
Foeniculum vulgare Miller (Apiaceae)	Fennel	شومر	Seeds	Decoction	1 teaspoon of the seeds is added to a cup of hot mint Mix 1 kg of fenugreek, 0.5 kg anise, 250g nigella and fennel Add 1/2 teaspoon of nigella, fenugreek, fennel, and common mallow to a cup of water	1 cup daily until recovery drinkglass1-2timesdaily drink 1 cup daily before breakfast	3 (1.3%)	1(1%)
Juglans regia L. (Juglandaceae)	Wallnut	جوز بلدي	Fruits	Raw	Eaten raw	7 fruits are eaten daily until recovery		3 (3.1%)
Linum usitatissimum L. (Linaceae)	Common flax	كتان زهري	Seeds	Decoction, Raw	1 teaspoon of the seeds is added to a cup of yoghurt a decoction is prepared by adding 1 teaspoon of the dried flowers	1 cup daily until recovery	4 (1.7%)	2 (2.1%)
Majorana syriaca (L.) Rafin. (Lamiaceae)	Wild Thyme, Mother of Thyme	زعتر بري، صعتر، سعتر	Leaves	Decoction	A decoction is prepared from the plant A decoction is prepared from the plant with mint prepared as pastry	2 cups daily until recovery1 cup daily until recovery Eaten when available		9 (9.4%)
Malva sylvestris L Malvaceae	Common Mallow	خبيزة	Areal parts	Cooked decoction	Cooked with onions and olive oil A decoction is prepared by adding 1 teaspoon of the leaves to a cup of boiled water	Eaten after cooking when available 1 cup before breakfast	14 (6.0%)	1 (1.0%)
Matricaria aurea (L.) Sch. Bip. (Asteraceae)	Golden Cotula	بابونج	Areal Parts	Decoction	A decoction is prepared by adding 1 teaspoon of the plant to a cup of boiled water A decoction is prepared from the plant with parsley A decoction is prepared from 1.5 teaspoon of mint and golden Cotulla in a cup of water	Take 1 cup twice daily until recovery Take 1 cup daily for a short time	21 (9%)	15 (15.6%)
Mentha spicata L. (Lamiaceae)	Peppermint	نعنع بستاني	Leaves	Decoction	A decoction is prepared from the leaves decoction is prepared from the plant with Golden Cotulla and thyme	1-2 cups daily until recovery	4 (1.7%)	8 (8.3%)
Nigella sativa L. (Ranunculaceae)	Nigella, Black Cumin	حبة البركة، قزحة	Seeds	Raw, Decoction, Cooked	One teaspoon of the seeds are grinded and mixed with one teaspoon of honey Add one teaspoon of the grinded seeds to a cup of milk Mix 500 gm of the grinded seeds with 1 kg of Honey	2 teaspoons are taken daily before breakfast until recovery 1 cup daily until recovery	81 (34.9%)	29 (30.2%)

Botanical name (Family)	English common name	Arabic name	Part Plant used	Form of preparation	Mode of preparation	Administration	2011 Cohort group	2014 Cohort group
					Add 250 mg of the grinded seeds with 250 mg of olive oil to 500 mg of honey Raw Prepared as sweets	2-3 teaspoons daily 1 teaspoon is taken daily before breakfast until recovery		
Olea europaea L. (Oleaceae)	Olives	زيتون	fruits	Oil	Oil add salt to 1/2 cup of the oil Add 250 mg of the grinded seeds of nigella with 250 mg of olive oil to 500 mg of honey	Oil is applied to the place of surgery. until recovery 1/2 cup is taken daily before breakfast until recovery Take 2 teaspoons daily until recovery	5 (2.2%)	8 (8.3%)
Petroselinum sativum Hoffm. (Apiaceae)	Parsley	بقدونس	Areal Parts	Fresh, Decoction	Eaten fresh A decoction is prepared from the plant by adding the cutted areal parts to 6 cups of boiled water A decoction is prepared from the plant with golden cotula	Eaten daily 3 times until recovery 1 cup 3 times daily until recovery take 1 cup twice daily for a short time		5 (5.2%)
Phoenix dactylifera L. (Palmaea)	Date Palm	نخيل	Fruits	Fresh	Fresh	1 -7 fruit every day, or eat 3 fruits daily before breakfast until recovery	28 (12.1%)	31(32.3 %)
Punica granatum L. (Punicaceae)	Pomegranate	رمان، جلنار	Fruits	Juice, Fresh	Juice a juice is prepared from the fruits with lemon, sugar is added as required Dry peel and grind Fruits peels are dried, grinded then filled in capsules Dried peel are boiled in water	1-2 cups daily 3-4 cups daily 1/2 teaspoon daily before breakfast until recovery 1 capsule is swollen daily after Eating, 3 times daily I glass of dried boiled peel is taken daily before breakfast 1 cup 3 times a day after Eating during chemotherapy	12 (5.2%))	34 (35.4%)
Pyrus malus L. (Rosaceae)	Apple	تفاح	Fruits	Raw, Juice, Cooked	The apple peel is boiled with 1 teaspoon of curcum Vinegar is prepared from the fruits Juice is prepared from the plant	1 cup daily until recovery add 1 teaspoon to a cup of water daily until recovery drink I cup of the juice 2-3 times daily Eating 1 daily for 2 months	8 (3.4%)	2 (2.1%)

Botanical name (Family)	English common name	Arabic name	Part Plant used	Form of preparation	Mode of preparation	Administration	2011 Cohort group	2014 Cohort group
Crocus sativus L. (Iridaceae	Saffron	زعفران	Seeds	Decoction	A decoction is prepared from the seeds	1-2 cups are taken daily	3 (1.3%)	
Rosmarinus officinalis L. (Lamiaceae)	Rosemary	حصلبان، إكليل الجبل	Leaves	Decoction	A decoction is prepared from the plant by adding 1 teaspoon of the leaves either fresh or dried to a cup of water	1 cup daily until recovery	8(3.4%)	6 (6.3%)
Salvia fruticosa Mill. (Lamiaceae)	White Sage, Common Sage	مريمية	Areal parts, leaves	Decoction	A decoction is prepared from the areal parts, or can be added to tea a decoction is prepared from the plant and thyme	1 -3 scup daily until recovery drink glass daily in the afternoon	14 (6.0%)	15(15.6 %)
Sesamum indicum L. (Pedaliaceae)	Sesame	سمسم	Seeds	Raw	Mix 1 teaspoon of the seeds with one teaspoon of honey 1 teaspoon of the seeds is added to 1/2 L of water Mix 100 gram of the seeds with honey mix 1 kg of honey with 2 large teaspoon of nigella, sesame, and nuts	Eat once daily before breakfast 1-3 cups daily Take large teaspoon daily Take large spoon before breakfast daily	6 (2.6%)	3 (3.1%)
Tamarindus indica L. (Fabaceae)	Tamarin	تمر هندي	Fruits	Decoction	The pulp is soaked in hot water	1-2 cups daily until recovery	8 (3.4%)	1(1.0%)
Teucrium capitatum L (*T.polium* L) (Lamiaceae)	Cat Thyme	جعدة	Areal parts	Decoction, Mixture	A decoction is prepared from theplant by adding 1 teaspoon of the plant to boiled water Mix 1 kg of honey with 100 mg of Ginseng and Nigella	1 glass is taken daily before breakfast 1 teaspoon three times daily	15 (6.5%)	
Trigonella berythea Boiss. & Blanche (*T. foenum- graecum* L.) (Fabaceae)	Fenugreek Seed, Beiruth Fenugreek	حلبة	Seeds	Decoction	A decoction is prepared from the seeds by adding 1 teaspoon of the seeds to a cup of water Prepared as sweets	2-3 cups daily until recovery Eating	11 (4.7%)	11(11.5)
Zea mays L. (Poaceae)	Zea, Corn	ذرة	Seeds, leaves, Corn hair	Decoction, raw	Mix 1 kg of queen honey with 2 teaspoon of corn wheat Green leaves are boiled in water a decoction is prepared from the Corn hair with mint	1 teaspoon daily before breakfast 1 cup daily 1 cup daily until recovery	6 (2.6%)	1 (1%)
Zingiber officinale Rose. (Zingiberaceae)	Ginger	زنجبيل	Roots	Decoction	A decoction is prepared by adding 1 teaspoon to a cup of boiled water a decoction is prepared from a mix of the plant with ginger, turmeric and honey a decoction is prepared from a mix of the plant with ginger, nigella, and camel milk	1-2 cups daily until recovery 2 cups daily 1 glass daily before breakfast	19 (8.2%)	8 (8.3%)

Fig. 2. *Ephedra foeminea* Forssk. (Ephedraceae). Alanda is a wild low stalky Eurasian shrub growing in most of the West Bank area.

was lower than that reported previously in a previous study in Palestine probably due to study population size and area (Ali-Shtayeh et al., 2011).

With the exception of *Ephedra foeminea* (Alanda) which emerged as the most utilized plant product in the 2014 cohort of cancer patients, results are in consistent with previously recorded trends (Ali-Shtayeh et al., 2011). The case of "Alanda" or *Ephedra foeminea* (EF) is an important one, with significant implications for medical practitioners who are treating patients with cancer in regions such as Palestine. In this part of the world, traditional medicine is closely related to patients' health belief models and is an integral part of the socio-medical landscape among the Palestinian population (Ali-Shtayeh and Jamous, 2006; 2008; Ali-Shtayeh et al., 2014). EF is a low stalky Eurasian shrub (Fig. 2) which is ubiquitous in most of the West Bank area.

Until July 2011, Alanda was not reported in Traditional Arabic Palestinian Herbal Medicine among the Palestinian population; at least in the context of cancer care (Ali-Shtayeh and Jamous, 2006, 2008; Ali-Shtayeh et al., 2000, 2011). At that time (Dec 2013), a news program about EF was uploaded to YouTube, and it soon spread quickly and widely among internet users and local media. The story was of a farmer from the village of Tura in Jenin, Palestine. He described his battle with cancer, for which he had undergone surgery and chemotherapy until told by his oncologist that the cancer was no longer responding to treatment. At the time, a sheep in his flock became ill with what he described as a cancerous growth. A fellow country man advised him to feed the animal on EF. So he began to allow the animal to graze on EF vines which were growing wild behind his home. Two weeks later, the sheep's tumor "disappeared" , and he began to use the EF remedy himself. Within a short period of time he too was free from disease, and he claims that his oncologist "could not believe" the subsequent test results (https://www.youtube.com/watch?v=y_1VP5o4KwA). Following the first YouTube video-clip, a long list of reports and internet programs appeared in Arabic, in the Palestinian media, where the plant was portrayed as a miraculous anti-cancer herb in the YouTube-based medicine era. The plant was being mentioned more and more, in the media, among the public, health care providers, and researchers, gradually spreading from the Palestinian community residing in the Tura village, Jenin in the north of the West Bank to other Palestinian communities in the area (Fig. 3).

Our results show clearly an emergence of *E. foeminea* use from 0.0% in 2011–55.2% in August-October 2014. We found that 53 out

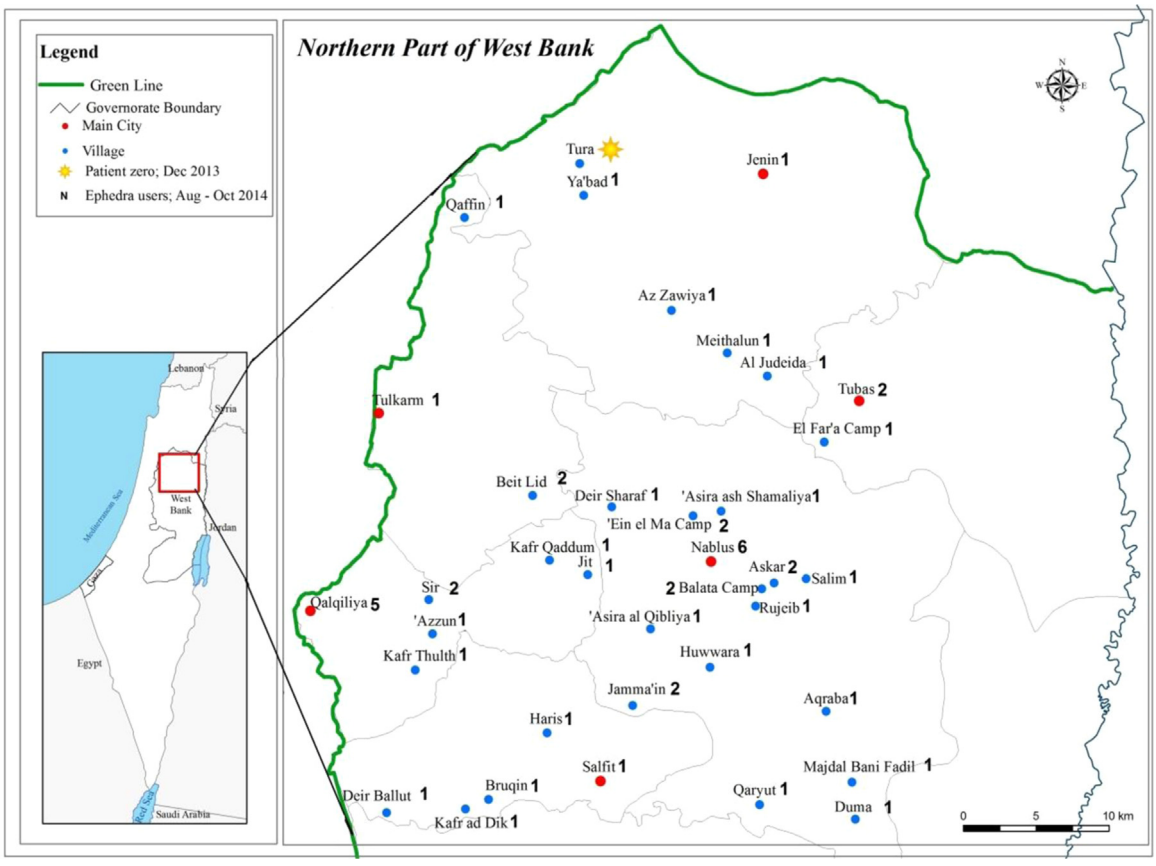

Fig. 3. Spread mapping of Ephedra use amongst Palestinian patients following media- mediated breaking news on patient zero in Tura Village, Jenin in northern West Bank, Palestine.

Table 6
Safety-related concerns for herbal products being used by patients with cancer.

Scientific name	Herb-drug interactions relevant in cancer treatment	Additional safety issues	Potential herb-related augmenting effect of chemotherapy
Allium cepa	Not found	None found	Caspase-dependent apoptosis is induced through mitochondrial pathway by up-regulating p53 protein, and subsequent Bax protein as well as by modulating Bcl-2 protein (Lee et al., 2014); colon and renal carcinogenesis are inhibited by organosulphur compounds (diallyl disulfide (DDS), S-allylcysteine (SAC) and Smethylcysteine (SMC)) (Fulda, 2008).
Allium sativum	Conflicting evidence about garlic's effect on CYP3A4. High doses may cause inhibition or induction of CYP 3A4 (Meijerman et al., 2006). Reduce activity of conventional antitumor drugs metabolized by cytochrome P3A4 and transported by P-glycoprotein including etoposide, paclitaxel, vinblastine, and vincristine (Piscitelli et al., 2002).	Increase possibility of excess bleeding in patients with bone marrow suppression due to antiplatelet activity (MacDonald et al., 2004; Beikang et al., 2014)	May prevent and reduce chemotherapy-induced mucositis through antiinflamatory and antioxidant mechanisms (Stargrove et al., 2007).
Amygdalus communis	None found	None found	Not found
Amygdalus Korschinskii	None found	None found	Not found
Arum palaestinum	None found	None found	Four flavonoid compounds (luteolin, chrysoeriol, isoorientin, isovitexin) isolated from the plants showed significant high antiproliferative activity against different human carcinoma cell lines (Farid et al., 2015).
Camellia sinensis	Prohibit the remedial effect of bortezomib and other boronic acid-based proteasome inhibitors by polyphenols (Golden et al., 2009); epigallocatechin gallate (EGCG) may impede the transport of irinotecan and its metabolite SN-38 into biliary elimination, resulting in span of their half-life leading to increase toxicity (Lin et al., 2008); OATP transporters can be inhibited by ECG and ECGC eg., etoposide, methotrexate, paclitaxel (Roth et al., 2011); extract increase the bioavailability of tamoxifen, simvastatin, and diltiazem may be by inhibition of CYP3A enzyme and/or (*p*-gp) (Ezzeldin et al., 2015)	Increase possibility of excess bleeding in patients with bone marrow suppression due to antiplatelet activity (Babu and Liu, 2008)	Polyphenols possess anticancer and antiprolifrative activity against cervical cancer (Krstic et al., 2015).
Cassia senna	None found	None found	Suppression of prostate tumor growth in vivo model using testosterone and N-methyl N-nitrosourea for induction of prostate carcinogenesis (Kumar et al., 2010).
Citrullus colocynthis	None found	Ethanolic extract of the plant might induce hepatocyte necrosis and liver fibrosis in rats due to the toxic effects on liver cells (Dehghani, and Panjehshahin, 2006)	None found
Citrus limon	None found	None found	Nanovesicles isolated from *Citrus lemon* activate a TRAIL-mediated apoptotic cell death leading to inhibition of cancer cell proliferation in different tumor cell lines (Raimondo et al., 2015)
Commiphora myrrha	None found	None found	Inhibit cell proliferation and possess cytotoxic effect against human gynecologic cancer cells.
Coridothymus capitatus	None found	None found	High cytotoxic activity against breast cancer cell line (MCF-7) (Hussein et al., 2014)
Crataegus aronia	None found	Inhibition of thromboxane A2 biosynthesis, increase risk of bleeding (Basch et al., 2012)	Significant cytostatic activity in monocultures and co-cultures (Kmail et al., 2015)
Crocus sativus	None found	None found	Antitumor and cytostatic activity against different cell line (Samarghandian et al., 2010; Noureini and Wink, 2012; Malaekeh-Nikouei et al., 2013; Samarghandian and Shabestari, 2013; Geromichalos et al., 2014; Kim et al., 2014; Rezaee et al., 2014; Rastgoo et al., 2013)
Cuminum cyminum	None found	Increase possibility of bleeding in patients with bone marrow suppression due to antiplatelet activity (Sowbhagya, 2013)	Seed extract showed anticancer activity against Colon Cancer cell lines (Prakash and Gupta, 2014)
Curcuma longa	Conflicting evidence about CYP3A4 suppression increased blood levels and toxicity of etoposide (Yue et al., 2012); increases toxicity of etoposide, paclitaxel, vinblastine and vincristine by inhibition of s P-glycoprotein activity (Appiah-Opong et al., 2007; Raucy, 2003); preventing cell death by opposing etoposide (Saleh et al., 2012)	Increase possibility of bleeding in patients with bone marrow suppression due to inhibition of platelet aggregation (Srivastava, 1989)	Curcumin Inhibits FA/BRCA pathway which leads to reverses cisplatin resistance in cisplatin-resistant lung cancer cells (Chen et al., 2015); curcumin showed cytotoxic activity to Dalton's lymphoma cells and lymphocytes (Kuttan et al., 1985)
Daucus carota	None found	None found	Falcarinol combined with anti-tumor agents have differential interactions on apoptosis and cellular

Table 6 (*continued*)

Scientific name	Herb-drug interactions relevant in cancer treatment	Additional safety issues	Potential herb-related augmenting effect of chemotherapy
			proliferation in human lymphoid leukaemia cell lines (Zaini et al., 2015); oil extract fractions possess potential anti-cancer activity on the human breast adenocarcinoma cell lines (Shebaby et al., 2014)
Ephedra foeminea	None found	None found	None found
Ferula asafoetida	None found	Might cause excess bleeding in patients with bone marrow suppression due to possible anticoagulant activity (Heck et al., 2000)	Galbanic acid exerts anti-tumor activity in association with anti-angiogenic and anti-proliferative actions (Kim et al., 2011)
Foeniculum vulgare	Inhibits CYP3A4 activity; might increase toxicity of chemotherapeutic medication (etoposide, paclitaxel, vinblastine, and vincristine) (Subehan et al., 2008); Acquires estrogenic activity, might reduces tamoxifen activity in estrogen responsive tumors (Leung and Foster, 1996)	Increase possibility of bleeding in patients with bone marrow suppression due to antiplatelet activity (Tognolini et al., 2007)	Plant extract possess antitumor, and cytotoxic activity (Pradhan et al., 2008)
Juglans regia	None found	None found	In vitro studies of cytotoxic activity (Salimi et al., 2012; Li et al., 2013; Salimi et al., 2014)
Linum usitatissimum	None found	Reduces tendency to platelet aggregation, might lead to excess bleeding in patients with bone marrow suppression (Basch et al., 2007)	Enhance trastuzumab (TRAS) tumor- reducing effects (Mason et al., 2010); significant inhibition of cell vitality and proliferation of human breast cancer cell lines MCF7 (Szewczyk, et al., 2014)
Majorana syriaca	None found	None found	Cytotoxic activity against P388 cells (Hirobe et al., 1998)
Malva sylvestria	None found	None found	None found
Matricaria aurea	Prohibits multiple CYP450 isoenzymes (3A4, 2D6, and 2C9) and may increase toxicity of chemotherapeutic medication (i.e., etoposide, paclitaxel, vinblastine, vincristine, and cyclophosphamide) (Ganzera et al., 2006); Contradictory results found in the literature focused on Cyp2D6 inhibition and the chemotherapeutic drug tamoxifen effectiveness (Cronin-Fenton et al., 2014)	Increase antiplatelate activity of warfarine, might lead to bleeding (Segal and Pilote, 2006)	None found
Mentha spicata	None found	None found	None found
Nigella sativa	None found	Reduce coaggulation, which mught lead to excess bleeding in patients with bone marrow suppression (Zaoui et al., 2002)	In addition the extract of the plant has also thymoquinone from *Nigella sativa* augmented the anticancer effect of gemcitabine and oxaliplatin in pancreatic cancer (Banerjee et al., 2009); antitumor activity against different human carcinoma cell lines including pancreatic cancer (Chehl et al., 2009), colon cancer (Salim and Fukushima, 2003), breast cancer (Effenberger et al., 2010) among others; extract has a strong immunomodulatory and interferon-like activity, it inhibits the progression of tumor and endothelial cell, and reduces the production of the angiogenic protein fibroblastic growth factor by tumor cells (Medenica et al., 1997).
Olea europaea	None found	Reduce coaggulation, which mught lead to excess bleeding in patients with bone marrow suppression (Petroni et al., 1995)	In vitro studies of cytotoxic activity (Juan et al., 2008; Bouallagui et al., 2011; Reyes-Zurita et al., 2011; Busnena et al., 2013)
Petroselinum sativum	None found	None found	Plant extract possess anticancer activity against HepG2 cells (Farshori et al., 2014)
Phoenix dactylifera	None found	None found	D-glucan from dates has shown antitumour activity (Ishurd et al., 2004)
Pimpinella anisum	Not found	None found	None found
Punica granatum	None found	None found	In vitro studies of cytotoxic and antitumor activity (Jeune et al., 2005; Banerjee et al., 2012; Jayakumar et al., 2012; Joseph et al., 2012; Bekir et al., 2013; Joseph et al., 2013)
Pyrus malus	None found	None found	Cytotoxic activity of volatile oil obtained from fresh leaves to animal and human cancer cell lines (Walia et al., 2012)
Rosmarinus officinalis	Inhibit CYP1A2 and CYP3A4 activities (Offord et al., 1997); increase the intracellular accumulation of vinblastine and dexorubicin in drug-resistant human breast cancer cells (MCF-7) leading to increased availability of the drugs for bioactivity (Plouzek et al., 1999)	Not found	Carnosic acid is known to exhibit effective anticancer activity against various cancer cell lines derived from human malignant tissues (leukaemia, breast, prostate, lung and liver) (Yesil-Celiktas et al., 2010)
Salvia fruticosa	None found	None found	Inhibit cell proliferation in HCT15 cell lines derived from human colon carcinoma (Xavier et al., 2009).
Sesamum indicum	Inhibit CYP3A4 activity in a concentration dependent manner, prevent induction of CYP3A4	None found	Promoting cancer cell proliferation and decreasing apoptosis (Sacco et al., 2007).

Table 6 (*continued*)

Scientific name	Herb-drug interactions relevant in cancer treatment	Additional safety issues	Potential herb-related augmenting effect of chemotherapy
	by interfering with the co-regulators of PXR (Lim et al., 2012); possesses estrogenic activity, decrease chemotherapeutic drug tamoxifen activity in estrogen responsive tumors (Sacco et al., 2007)		
Tamarindus indica	Possibly reduce activity of cyclophosphamide, vinblastine, or may chemosensitize malignant cells to paclitaxel	Interact with aspirin and anticoagulant drugs, thus increase risk of bleeding (Isha et al., 2012)	Co-encapsulation of doxorubicin with galactoxyloglucan nanoparticles isolated from the plant have greater potential compared to the doxorubicin as targeted drug delivery nanocarriers for loco regional cancer chemotherapy applications (Joseph et al., 2014); cytotoxic activity against human amniotic epithelial cell line (FL-Cells) (Al-Fatimi, et al., 2007)
Teucrium capitatum	None found	Active compounds (e.g., furan-containing diterpenoids) are oxidized by CYP450 isozyme 3A4 to reactive metabolites that bind to proteins, deplete cellular glutathione and protein thiols, and induce membrane disruption and hepatocyte apoptosis (Lekehal et al., 1996; Loeper et al., 1994; Fau et al., 1997)	Diterpenoids possess anti-cancer chemosensitizer activity (Corea et al., 2004; Michaelis et al., 2000)
Trigonella berythea	None found	Reduce platelet activity which possibly leading to excess bleeding in patients with bone marrow suppression (Bordia et al., 1997)	In vitro studies of cytotoxic activity (Alsemari et al., 2014)
Zea mays	None found	None found	None found
Zingiber officinale	None found	Decrease platelet aggregation, might inhibit thromboxane synthetase, thus increase bleeding (Ge et al., 2014)	Leaf extract reduced the cell viability and induced apoptosis in human colorectal cancer cells (HCT116, SW480 and LoVo cells) (Parket al., 2014)

of 100 patients with cancer reported using EF, only a few months after the spread of the Alanda (EF) story, where the plant was portrayed in the media as a miraculous anti-cancer herb (Fig. 3). Interestingly, a recent study (Jan –June 2015) on herbal remedies use among breast cancer patients in the Palestinian West Bank has found *Ephedra alata*. (?) to be the most commonly used (45.7%) herbal remedy among this group of patients (Jaradat et al., 2016). The wide spread use among breast cancer patients was similarly attributed to a recent publicizing and portraying of the plant in the local media as an effective cancer herbal remedy. However, *E. alata* Decne is a rare desert plant restricted to southern Negev and cannot be found in the Palestinian West Bank, and therefore was most likely to be a misidentification of *E. foeminea* which is a very common wild plant in the same area.

A close relative of the species, *Ephedra sinica* (Ma Huang), is a popular medicinal remedy used for a number of clinical conditions by practitioners of traditional Chinese medicine (Lee, 2011). Ma Huang has been found to contain ephedrine alkaloid components which have been associated with significant cardiovascular and central nervous system toxicities. Following a series of cases in which severe complications and even death resulted from its use, many countries, including the USA, started to ban the import or sale of ephedra (Woolf et al., 2005). Interestingly, none of the patients using Alanda who participated in our study reported any potential harmful effects of the plant. Extensive search of the TAPHM, revealed no relevant information on *E. foeminea.* Interestingly, *E. alata* (most likely a misidentification of *E. foeminea*) has been found to have significant cytostatic effects in mono and co-cultures of HepG2 and human THP-1 indicating that the claimed anti-cancer effects of the plant extract might be mediated in part through cytostatic effects (Kmail et al., 2015).

CAM modalities such as herbal medicine may be of benefit in certain cases but are not without potential risks, including adverse herb-drug interactions, concurrent use of herbs may mimic, magnify, or oppose the effect of drugs (Fugh-Berman, 2000). Traditional herbal medicine is often perceived by patients, especially in communities with high affinity for traditional medicine, 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 back yards and other unsupervised venues. The widespread popularity of Alanda was not supported by any scientific findings, or even teachings of TAPHM, but rather spread by the media (e.g., YouTube video).

The story of Alanda is becoming the rule and not the exception. This is especially true in regions where traditional medicine is an integral part of the medical culture. In these societies, social norms often shift between concepts of the individual and identification with the collective. Therefore, the values of the group, such as how the society views the use of traditional herbal medicine should be considered as part of the communal health belief model.

3.7. Safety-related concerns

The use of herbal medications is prevalent ($>90\%$) among Palestinian cancer patients who are taking prescription medications. Yet few clinical studies have systematically shown potential herb-drug-disease interactions between herbs and medications, especially with drugs that contain several herbs (Afifi et al., 2010; Hu et al., 2005; Wirth et al., 2005;Tascilar et al., 2006; Meijerman et al., 2006; Birdsall et al., 2014).

In this study of the 40 herbal products identified a total of 33 herbs (82.5%) were found to be associated with three categories of safety-related concerns (Table 6): herb-drug interactions (8 herbs, 20%); toxic effects of the herbal components (16 herbs; 40.0%); and Effects on antitumor activity by alterations in the response of cancer cells to chemotherapy either through synergy or increased chemosensitivity (31 herbs; 77.5%).

3.7.1. Herb-drug interactions

Several potentially negative herb-drug interactions were identified among herbal products used by Palestinian cancer patients

who are simultaneously taking prescription medications. These were mediated primarily through the cytochrome P450 enzymes; either by induction or inhibition of CYP3A4. The induction of CYP can cause a decline in the bioavailability and subsequently the effectiveness of anti-tumor agents, while the inhibition of the enzyme can raise the possibility of toxicity (DeLeve, 2003). Additional herb-drug interactions effects on factors such as intestinal P-glycoprotein (*p*-gp), which inhibits drug absorption and alter the bioavailability of anticancer drugs. Herb-drug interactions may include pharmacodynamic (PD) and/or pharmacokinetic (PK) components. The later interaction may also lead to decreased or increased plasma levels of the drug and thus reduction in efficacy or unexpected toxicity. Sever herbs including the St. John's Wort are thought to induce or inhibit the metabolism of drugs that are substrates of CYP450s and/or (*p*-gp), UDP-Glucuronosyltransferase (UGT) enzymes, and other drug metabolism pathways (Fasinu et al., 2012; Mannel, 2004; Birdsall and Weiss, 2014). Herb-drug interactions pose an extensive risk to the cancer patient population (Table 6), it could lead to increased risk for adverse events such as bleeding (e.g., *A. sativum*, and *Oxalis europea*) or hepatoxicity (e.g., *Citrullus colocynthis* and *Trichosporon capitatum*) (Melchardt, 2014). Additionally, some herbs may have estrogenic effects (e.g., *Foeniculum vulgare,* and *Sesamum indicum*), which would be a contraindication in hormone-sensitive cancers including breast, prostate, womb and kidney cancers (Leung and Foster, 1996; Sacco et al., 2007; Birdsall et al., 2014).

Curcuma longa (Yue et al., 2012), *Rosmarinus officinalis* (Offord et al., 1997) *Matricaria aurea* (Ganzera et al., 2006), *Allium sativum* (Meijerman et al., 2006), *Foeniculum vulgare* (Subehan et al., 2008), and *Sesamum indicum* (Lim et al., 2012) have shown to inhibit CYP3A4 enzyme activity resulting in increase in the toxicity of drugs metabolized by this enzyme including chemotherapeutic agents e.g., etoposide, paclitaxel, vinblastine and vincristine. *Allium sativum* (Piscitelli et al., 2002), and *Curcuma longa* (Appiah-Opong et al., 2007; Raucy, 2003) inhibit P-glycoprotein activity and possibly increase the bioavailability of anticancer drugs such as etoposide, paclitaxel, vinblastine, and vincristine.

The polyphenols of *Camellia sinensis* may prohibit the remedial effect of bortezomib and other boronic acid-based proteasome inhibitors (Golden et al., 2009); whereas epigallocatechin gallate (EGCG) may impede the transport of irinotecan and its metabolite SN-38 into biliary elimination, resulting in span of their half-life leading to increase toxicity (Lin et al., 2008), and inhibit organic anion transporting polypeptides (OATP) e.g., etoposide, methotrexate, paclitaxel (Knop et al., 2015). Also green tea extract increases the bioavailability of tamoxifen, simvastatin, diltiazem, and irinotecan possibly by inhibition of CYP3A enzyme and/or (*p*-gp) (Ezzeldin et al., 2015). In vitro evidence suggests that *Foeniculum vulgare* (Leung and Foster, 1996) and *Sesamum indicum* (Sacco et al., 2007) have shown also to decrease tamoxifen activity in estrogen responsive tumors. *Rosmarinus officinalis* increased the intracellular accumulation of vinblastine and dexorubicin in drug-resistant human breast cancer cells (MCF-7) leading to increased availability of the drugs for bioactivity (Plouzek et al., 1999).

3.7.2. Direct herb-related toxicity

Sixteen of the medicinal plants reported in this study were found to have direct toxic effects. *Camellia sinensis* (Babu and Liu, 2008), *Allium sativum* (Beikang et al., 2014), *Cuminum cyminum,* (Sowbhagya, 2013) *Foeniculum vulgare* (Tognolini et al., 2007), *Trigonella berythea* (Bordia et al., 1997), *Nigella* sativa (Zaoui et al., 2002), and *Olea europaea* (Petroni et al., 1995) have shown to increase risk of bleeding with anticoagulant and antiplatelet treatment. *Curcuma longa* (Srivastava, 1989), *Zingiber officinale* (Beikang et al., 2014), *Ferula asafetida* (Heck et al., 2000), and *Linum usitatissimum* (Basch et al., 2007) have shown to impair platelet aggregation. *Teucrium capitatum* (Fau et al., 1997) and *Citrullus colocynthis* (Dehghani, and Panjehshahin, 2006) have hepato-toxic effects.

3.7.3. Effects on antitumor activity

Thirty one of the medicinal plants reported in this study were found to promote and enhance the cytotoxic activity of conventional anticancer antitumor drugs (Table 6). This was attributed to either the synergistic interaction with the conventional drug or chemosensitization of the cancer cells. Curcumin from *Curcuma longa* reverses cisplatin resistance in cisplatin-resistant lung cancer cells by inhibiting FA/BRCA pathway (Chen et al., 2015); *Linum usitatissimum* enhances the antitumor effects of trastuzumab (TRAS) tumor-reducing effects in breast cancer cell lines (Mason et al., 2010); thymoquinone from *Nigella sativa* augmented the anticancer effect of gemcitabine and oxaliplatin in pancreatic cancer (Banerjee et al., 2009). In addition the extract of the plant has also a strong immunomodulatory and interferon-like activity; it inhibits the progression of tumor and endothelial cell, and reduces the production of the angiogenic protein fibroblastic growth factor by tumor cells (Medenica et al., 1997). Increased cell death has been observed with exposure of ginger leaf to human colorectal cancer cells (HCT116, SW480 and LoVo cells) (Park et al., 2014); galbanic acid isolated from *Ferula asafoetida* exerts anti-cancer activity in association with anti-angiogenic and anti-proliferative actions (Kim et al., 2011); Falcarinol (a polyacetylene isolated from *Daucus carota*) showed a significant induction of apoptosis of Human Lymphoid Leukaemia Cell Line (Jurkat cells) with a Death Receptor 5 agonist (DR5), while CCRF-CEM cells showed only an additive response (Zaini et al., 2015); nanovesicles isolated from *Citrus lemon* have shown to activate a TRAIL-mediated apoptotic cell death leading to inhibition of cancer cell proliferation in different tumor cell lines (Raimondo et al., 2015). Herbal compounds also have been found to prevent and reduce chemotherapy-induced mucositis through anti-inflammatory and antioxidant mechanisms (e.g. *Allium sativum*) (Stargrove et al., 2007), and promote cancer progression (e.g., *Sesamum indicum*) by negating the inhibitory effect of tamoxifen, and promote cancer cells proliferation and decrease apoptosis in breast cancer (Sacco et al., 2007).

Although the possibility for an enhanced response of tumor cells to anticancer therapies may appear desirable, however, if proven true, the dose density of anticancer therapies need to be adjusted, since higher doses of therapeutics may inevitably result in an increased risk of toxicity, and should be avoided (Singletary et al., 2004).

The majority of the results regarding herb-drug interactions for the 33 plants identified in this study are based on preclinical or limited clinical trials. This makes it difficult for patients and their oncology health care providers to make an informed, evidence-based decision on the use of these plants. A negative approach for this would be to make a recommendation against the use of all medicinal plants during conventional antitumor treatment. However, such an approach might decrease disclosure of this practice among cancer patients, especially in populations in which the use of medicinal plants in health care is very common. A more reasonable and practical approach is to educate cancer physicians and other health care providers about CAM medicinal plants use, providing them with the tools for better communication with their patients. The use of medicinal plants for which there is no evidence of activity, or there are significant safety related issues should be discouraged.

4. Conclusions

Use of CAM especially herbal medicine in cancer is highly prevalent in Palestine. This study has demonstrated the role of the

media on the emergence of new CAM herbal therapies among cancer patients in Palestine, and discussed its potential implications on patients and for oncologists who are treating them. Some of the most widely used herbal medicines by cancer patients in the present work are known to interact with conventional anticancer drugs. Hence, the disclosure of the use of herbal remedies by patients to health professionals with sufficient training in CAM use is important for the later in order to assess whether there are any possible herbal drug interactions and/or harmful drug reactions.

Conflict of interest statement

The authors have no conflict of interest.

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